Pharmaceutical Approval Update

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Milnacipran HCl (Savella) Film-Coated Tablets for Fibromyalgia

Manufacturer: Forest Laboratories, New York/Cypress Biosciences, Inc., San Diego

Indication: Milnacipran is indicated for the management of fibromyalgia. It is not approved for use in pediatric patients.

Drug Class: The drug acts like medications that are used to treat depression and other psychiatric disorders. Milnacipran is a selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI). Its chemical formula is (1R,2S)-rel-2-aminomethyl-N,N-diethyl-1-phenylcyclopropene- carbonamide HCl. Its molecular weight is 282.8 daltons.

Uniqueness of Drug: As a member of the SNRI class, milnacipran is used in Europe and Asia to relieve symptoms of depression. However, it has also been effective in relieving the chronic pain associated with several types of illnesses, including fibromyalgia. By blocking the reuptake of neurotransmitters NE and 5-HT (two of the primary hormones that are involved in depression and sensations of severe and chronic pain), more neurotransmitters are left in the synaptic cleft for a greater effect on the neurons in the hippocampus to control mood and pain sensation.

Boxed Warning: Suicidality and antidepressant drugs. Milnacipran is a SNRI, similar to some drugs used to treat depression and other psychiatric disorders. Antidepressants increased the risk, compared with placebo, of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of such drugs in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies have not shown an increased risk of suicidality with antidepressants compared with placebo in adults beyond age 24, and there was a reduction in risk with antidepressants, compared with placebo, in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide.

Patients of all ages who are started on milnacipran should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Milnacipran is not approved for use in the treatment of MDD or for use in pediatric patients.

Warnings and Precautions:
Suicide risk. Milnacipran is similar to some drugs used for the treatment of depression and other psychiatric disorders. Patients, both adult and pediatric, with depression or other psychiatric disorders may experience worsening of their depression and/or the emergence of suicidality or unusual changes in behavior, whether or not they are taking these medications. This risk may persist until significant remission occurs.

Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants, including drugs that inhibit the reuptake of NE and/or 5-HT, may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

In placebo-controlled clinical trials of adults with fibromyalgia, among patients who had a history of depression at the start of treatment, the incidence of suicidal ideation was 0.5% with placebo, 0% with milnacipran 100 mg/day, and 1.3% with milnacipran 200 mg/day. No suicides occurred in the short-term or longer-term (up to one year) fibromyalgia trials.

There was considerable variation in risk of suicidality among drugs but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug versus placebo), however, was relatively stable within age strata and for all indications.

Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with drugs inhibiting the reuptake of NE and/or 5-HT for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Changing the therapeutic regimen, including discontinuing the medication, might be considered if patients are experiencing worsening depressive symptoms or are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe or abrupt in onset or were not part of the patient’s presenting symptoms.

If treatment is discontinued because of worsening depressive symptoms or emergent suicidality, the medication should be tapered as rapidly as feasible. It should be recognized, however, that abrupt discontinuation can produce withdrawal symptoms.

Serotonin syndrome. The development of a potentially life-threatening serotonin syndrome may occur with agents that inhibit serotonin reuptake, including milnacipran, particularly with the concomitant use of serotonergic drugs, including triptans and tramadol (Ultram, Ortho-McNeil), and with drugs

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that impair metabolism of 5-HT, including monoamine oxidase (MAO) inhibitors. Symptoms may include changes in mental status (agitation, hallucinations, coma), autonomic instability (tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (hyperreflexia, incoordination), and gastrointestinal (GI) symptoms (nausea, vomiting, diarrhea). The concomitant use of milnacipran with MAO inhibitors is contraindicated.

Effects on blood pressure. Inhibition of the reuptake of NE and 5-HT can lead to cardiovascular effects. SNRIs, including milnacipran, have been associated with reports of increases in blood pressure (BP).

In placebo-controlled trials, among fibromyalgia patients who did not have hypertension at baseline, approximately twice as many patients in the milnacipran arms became hypertensive at the end of the study (with a systolic BP of 140 mm Hg or higher or a diastolic BP of 90 mm Hg or higher) compared with placebo patients: 7.2% of patients receiving placebo versus 19.5% of patients receiving milnacipran 100 mg/day and 16.6% of patients receiving milnacipran 200 mg/day.

Among patients who met systolic criteria for pre-hypertension at baseline (with a systolic BP of 120 to 139 mm Hg), more milnacipran patients became hypertensive at the end of the study compared with placebo patients: 9% with placebo versus 14% with milnacipran 100 mg/day and 200 mg/day.

Among fibromyalgia patients who had hypertension at baseline, more patients in the milnacipran arms experienced an increase of more than 15 mm Hg in systolic BP than placebo patients at the end of the study: 1% of placebo patients versus 7% of patients in the milnacipran 100-mg/day arm and 2% in the milnacipran 200-mg/day arm.

Similarly, more patients who were hypertensive at baseline and who used milnacipran had diastolic BP increases above 10 mm Hg than placebo patients at the end of the study: 3% of placebo patients versus 8% of patients in the milnacipran 100-mg/day and 6% in the milnacipran 200-mg/day arms.

Sustained increases in systolic BP of 15 mm Hg or more on three consecutive post-baseline visits occurred in 2% of placebo patients, in 9% of patients receiving milnacipran 100 mg/day, and in 6% of patients receiving milnacipran 200 mg/day. Sustained increases in diastolic BP (an increase of 10 mm Hg or more on three consecutive post-baseline visits) occurred in 4% of patients receiving placebo, in 13% of patients receiving milnacipran 100 mg/day, and in 10% of patients receiving milnacipran 200 mg/day.

Effects on heart rate. SNRIs have been associated with reports of an increase in heart rate. The heart rate should be measured before patients begin treatment and periodically throughout treatment. Pre-existing tachycardias and other cardiac disease should be treated before milnacipran therapy starts. For patients who experience a sustained increase in heart rate while receiving milnacipran, either a dose reduction or discontinuation should be considered.

Seizures. Milnacipran should be prescribed with care in patients with a history of a seizure disorder.

Hepatotoxicity. In placebo-controlled fibromyalgia trials, increases in the number of patients treated with milnacipran who had mild elevations of liver enzymes (ALT or AST) (at one to three times the upper limit of normal [ULN]) were observed. Increases in ALT were more frequent in patients receiving 100 mg/day (6%) and 200 mg/day (7%), compared with patients who were treated with placebo (3%). In one patient receiving 100 mg/day (0.2%), the increase in ALT was more than five times the ULN but did not exceed 10 times the ULN. Increases in AST were more frequently observed with milnacipran 100 mg/day (in 3% of patients) and 200 mg/day (in 5% of patients) compared with placebo (in 2% of patients).

Discontinuation of treatment. Withdrawal symptoms have been observed in clinical trials following discontinuation of milnacipran, as with other SNRIs and selective serotonin reuptake inhibitors (SSRIs). During the marketing of milnacipran and other SNRIs and SSRIs, there were spontaneous reports of adverse events indicative of withdrawal and physical dependence occurring when patients discontinued these drugs, particularly when discontinuation was abrupt. Adverse events included dysphoric mood, irritability, agitation, dizziness, sensory disturbances (paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been severe.

Hyponatremia. Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including milnacipran. In many cases, hyponatremia appears to result from the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Abnormal bleeding. SSRIs and SNRIs, including milnacipran, may increase the risk of bleeding events. The concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin (Coumadin, Bristol-Myers Squibb), and other anticoagulants may elevate this risk.

Patients with a history of dysuria. Because of their noradrenergic effect, SNRIs (including milnacipran) can affect urethral resistance and micturition. In controlled trials of fibromyalgia, dysuria occurred more frequently in milnacipran patients (1%) than in placebo patients (0.5%).

Narrow-angle glaucoma. Because mydriasis has been reported in association with SNRIs and milnacipran, milnacipran should be used cautiously in patients with controlled narrow-angle glaucoma.

Use with alcohol. In clinical trials, elevated transaminase levels (ALT and AST) occurred in more milnacipran patients than in placebo-treated patients. Because milnacipran may exacerbate pre-existing liver disease, it should not be prescribed for patients with substantial alcohol use or evidence of chronic liver disease.

Allergy to coloring agents. Milnacipran contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in susceptible persons such as those with aspirin hypersensitivity.

Dosage and Administration: The recommended dose of milnacipran is 100 mg/day (50 mg twice daily). Doses should be titrated according to the following schedule: day 1, 12.5 mg once daily; days 2 to 3, 25 mg/day (12.5 mg twice daily); days 4 to 7, 50 mg/day (25 mg twice daily); and after day 7, 100 mg/day (50 mg twice daily).

According to individual patient response, the dose may be increased to 200 mg/day (100 mg twice daily). Doses above
200 mg/day have not been studied. The dose should be tapered and should not be abruptly discontinued after extended use. Milnacipran is taken orally with or without food, although taking this drug with food may improve its tolerability.

**Patients with renal insufficiency.** No dosage adjustment is necessary in patients with mild renal impairment. Milnacipran should be used with caution in patients with moderate renal impairment. For patients with severe renal impairment (a creatinine clearance of 3 to 29 mL/minute), the maintenance dose should be reduced by 50% to 50 mg/day (25 mg twice daily). Based on individual patient response, the dose may be increased to 100 mg/day (50 mg twice daily). Milnacipran is not recommended for patients with end-stage renal disease.

**Patients with hepatic insufficiency.** No dosage adjustment is necessary for patients with hepatic impairment. As with any drug, caution should be exercised in patients with severe hepatic impairment.

**Commentary:** Fibromyalgia, a chronic condition characterized by widespread pain and decreased physical function, affects as many as six million people in the U.S. Milnacipran differs from other existing SNRIs, such as venlafaxine (Effexor, Wyeth), which work mostly by preventing the reuptake of serotonin (5-HT). Although SNRIs do stop the reuptake of norepinephrine (NE), they work to a much less powerful extent on this neurotransmitter. Milnacipran however, works almost equally on both NE and 5-HT, providing relief of both pain and depression.

Milnacipran also differs from other traditional antidepressants, in that it is not associated with severe reactions associated with those medications, such as weight gain, cardiac problems, and sexual side effects.

**Sources:** www.fda.gov; www.savella.com

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**Calcitriol Ointment (Vectical) for Plaque Psoriasis**

**Manufacturer:** Galderma Laboratories, Fort Worth, Texas

**Indication:** Calcitriol ointment at a dose of 3 mcg/g is indicated for the topical treatment of mild-to-moderate plaque psoriasis in patients 18 years of age and older. This product should not be applied to the eyes, lips, or facial skin.

**Drug Class:** The ointment is a vitamin D analogue that is applied to the skin. The chemical name of the active ingredient is (5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol. The molecular weight is 416.64 daltons.

**Uniqueness of Product:** This is the only vitamin D3 ointment that has been well tolerated in clinical trials even when used on sensitive skin fold areas.

**Warnings and Precautions:**

**Effects on calcium metabolism.** In controlled clinical trials involving participants undergoing laboratory monitoring, hypercalcemia was observed in 24% of subjects exposed to the active drug and in 16% of subjects exposed to the vehicle. However, the increases in calcium and albumin-adjusted calcium levels were less than 10% above the ULN. If aberrations in parameters of calcium metabolism occur, treatment should be discontinued until these parameters have returned to normal. The effects of the ointment on calcium metabolism after a duration longer than 52 weeks have not been evaluated. Increased absorption may occur with occlusive use.

**Ultraviolet light exposure.** Animal data suggest that the vehicle of calcitriol ointment may enhance the ability of ultraviolet radiation to induce skin tumors. Subjects who apply the ointment to exposed skin should avoid excessive exposure of the treated area to either natural or artificial sunlight, including tanning booths and sun lamps. Physicians may wish to limit or avoid use of phototherapy in patients who use the product.

**Unevaluated uses.** The safety and effectiveness of calcitriol ointment in patients with known or suspected disorders of calcium metabolism or in patients with erythrodermic exfoliative or pustular psoriasis have not been evaluated.

**Dosage and Administration:** The ointment is applied to affected areas twice daily, in the morning and evening. The maximum weekly dose should not exceed 200 g. Calcitriol ointment is not indicated for oral, opthalmic, or intravaginal use.

**Commentary:** Psoriasis is a chronic skin disorder that affects 2% to 3% of the U.S. population. Characterized by thick, red, scaly patches of skin, it is caused by an abnormally high growth rate of skin cells that form thick, dry scales (plaques). Psoriasis is also associated with other conditions such as diabetes, heart disease, and obesity.

Because psoriasis is a chronic disease, topical products that are safe for extended use must fit within overall, long-term regimens. The availability of this product, which is a form of vitamin D3 with three alcohol groups, has proved safe and well tolerated for up to 52 weeks of continuous use in treating mild-to-moderate disease. A safe, effective long-term therapy is critical for improving overall outcomes for these patients. The other vitamin D topical agent available for treating psoriasis is calcipotriol ointment or cream (Dovonex).

**Sources:** www.fda.gov; www.vectical.com

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**Degarelix Subcutaneous Injection for Prostate Cancer**

**Manufacturer:** Ferring Pharmaceuticals, Inc., Parsippany, N.J.

**Indication:** Degarelix is a gonadotropin-releasing hormone (GnRH) receptor antagonist that is designed to treat advanced prostate cancer.

**Drug Class:** This sterile, lyophilized powder for subcutaneous (SQ) injection contains degarelix (as the acetate) and mannitol. This synthetic linear decapeptide amide contains seven synthetic amino acids, five of which are D-amino acids. The acetate salt of degarelix is a white to off-white amorphous powder of low density, as obtained after lyophilization.

The chemical name is D-alaninamide, N-acetyl-L-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-L-3-(3-pyridinyl)-D- alanyl-L-seryl-L-[[(4s)-hexahydro-2,6-dioxo-4-pyrimidinyl] carbonyl]amino]-L-phenylalanyl-4-[(aminocarbonyl)amino]-D- phenylalanyl-L-leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl. The molecular weight is 1,632.3 daltons.

**Uniqueness of Drug:** Degarelix is the only GnRH receptor antagonist approved by the FDA for treating hormonally sensitive late-stage prostate cancer. The drug binds reversibly to the pituitary GnRH receptors, thereby reducing the release
of gonadotropins and, consequently, testosterone. Unlike luteinizing hormone–releasing hormone (LHRH) agonists, degarelix achieves medical castration by binding reversibly to GnRH receptors on cells in the pituitary gland.

**Warnings and Precautions:**

*Use in pregnancy.* Degarelix is a Pregnancy Category X agent. Women who are or may become pregnant should not take degarelix.

*Effect on the QT and corrected QT interval.* Long-term androgen deprivation therapy prolongs the QT interval. Physicians should consider whether the benefits of androgen-deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (quinidine, procainamide) or Class III (amiodarone [Cordarone, Wyeth], sotalol [Betapace, Berlex]), antiarrhythmic medications. In a randomized, active-controlled trial comparing degarelix with leuprolide, periodic electrocardiograms were performed. Seven patients, three in the pooled degarelix group and four in the leuprolide 7.5-mg group, had a QTcF (Fridericia’s Correction Formula) of more than 500 milliseconds (msec). From the baseline evaluation to the end of the study, the median change for degarelix was 12.3 msec; for leuprolide, it was 16.7 msec.

*Laboratory testing.* Therapy with degarelix results in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotropic and gonadal functions conducted during and after degarelix may be affected. The therapeutic effect of degarelix should be monitored by periodically measuring serum concentrations of prostate-specific antigen (PSA). If PSA levels increase, serum concentrations of testosterone should be measured.

*Dosage and Administration:* Degarelix is indicated for SQ administration only and is not to be given intravenously. Treatment is initiated with a dose of 240 mg given as two injections of 120 mg each. The starting dose is followed by maintenance doses of 80 mg administered as a single injection every 28 days.

**Commentary:** Prostate cancer is known to grow in the presence of testosterone. Suppression of testosterone has been a treatment goal for advanced prostate cancer for many years. Surgical castration was the standard method of reducing testosterone levels from the 1940s until the mid-1980s, when the earliest forms of medical castration (LHRH agonists) were introduced. The use of GnRH receptor antagonists is an efficient way to stop the production of testosterone. The FDA’s approval of degarelix provides an effective alternative in the treatment of hormonally sensitive prostate cancer. The disease can be treated with immediate inhibition of the GnRH receptors, inducing rapid reduction of testosterone to castrate levels, and sustaining those levels over time, which are the goals of systemic therapy.

**Sources:** www.fda.gov; www.ferring.com