

Milnacipran Hydrochloride (Savella)

STEPS

September 9, 2009

RECOMMENDATION Milnacipran (Savella) to be **non-formulary**. It *may* be effective in treating fibromyalgia, but it has not been proven safer or more effective than any other medications used to treat fibromyalgia (FM). Since Milnacipran has FDA indication for FM, it should be treated similar to pregabalin (Lyrica) and duloxetine (Cymbalta), which also have FDA indication for FM. *Non-formulary and may be approved after trial of formulary options.*

Milnacipran Hydrochloride

(Savella®)

Forest Pharmaceuticals, Inc.

Introduction	<p>Milnacipran is a serotonin-norepinephrine reuptake inhibitor (SNRI) like Duloxetine and Venlafaxine. It is the third drug approved for Fibromyalgia. It is not approved in the USA for depression, although it has been used as an antidepressant in parts of Europe and Asia for more than 10 years.</p> <p>Milnacipran has a 3:1 ratio of norepinephrine to serotonin reuptake inhibition, without affecting the uptake of dopamine or other neurotransmitters.¹ Milnacipran is generally devoid of activity at the serotonergic, alpha and beta-adrenergic, muscarinic, histamine, dopamine, opiate, benzodiazepine, and GABA receptors. Pharmacology activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with many psychotropic drugs.¹</p>
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SAFETY =/—

Drug Interactions	Lithium, Epinephrine, Norepinephrine, Digoxin, clonidine, clomipramine, CNS-active drugs, MAOIs.
Pregnancy/ Lactation	Pregnancy Category C
Pediatric	It has not been studied in pediatrics
Elderly	<p>In controlled clinical studies with milnacipran, 402 patients were 60 years old or older. No differences in safety or efficacy were observed as compared to younger patients.</p> <p>As with all SNRIs and SSRIs, use with caution in the elderly.</p>
Renal/Hepatic Impairment	<p>Renal Impairment: MILD: No dosage adjustment Renal impairment: MODERATE: Use caution. Renal Impairment: SEVERE: Decrease dosage by 50%</p> <p>Hepatic Impairment: MILD: No dosage adjustment necessary. Milnacipran may aggravate pre-existing liver disease; it should not be use in patients with substantial alcohol use or evidence of chronic liver disease.</p>

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Contraindications	Monoamine Oxidase Inhibitors Uncontrolled Narrow-Angle Glaucoma
Precautions	<p>Suicide risk: as with all drugs in this class</p> <p>Serotonin Syndrome</p> <p>May increase blood pressure</p> <p>May increase heart rate: Milnacipran has not been specifically evaluated in patients with Cardiac rhythm disorders.</p> <p>Milnacipran has not been specifically evaluated in patients with seizure disorders.</p> <p>Hyponatremia</p> <p>Abnormal Bleeding</p> <p>Milnacipran has not been specifically evaluated in patients with mood disorders such as Mania or Hypomania.</p> <p><i>Caution is advised in use of milnacipran in patients with a history of dysuria, notably male patients with prostatic hypertrophy, prostatitis, and lower urinary tract obstructive disorders.</i></p>
TOLERABILITY =	
Adverse Reactions	Nausea, headache, constipation dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increased, dry mouth, and hypertension. (incidence ≥5% and twice that of placebo¹)
EFFICACY =/—	
FDA-approved indications	Fibromyalgia
Pharmacokinetics	<p>Pharmacology:</p> <p>The exact mechanism of the central pain inhibitory action of milnacipran and its ability to improve the symptoms of fibromyalgia in humans are unknown. Preclinical studies have shown that milnacipran is a potent inhibitor of neuronal norepinephrine and serotonin reuptake; milnacipran inhibits norepinephrine uptake with an approximately 3-fold higher potency in vitro than serotonin without directly affecting the uptake of dopamine or other neurotransmitters. Milnacipran has no significant affinity for serotonergic (5-HT₁₋₇), alpha- and beta-adrenergic, muscarinic (M₁₋₅), histamine (H₁₋₄), dopamine (D₁₋₅), opiate, benzodiazepine, and GABA receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Milnacipran has no significant affinity for Ca⁺⁺, K⁺, Na⁺, and CL⁻ channels and does not inhibit the activity of human monoamine oxidases (MAO-A and MAO-B) or acetylcholinesterase.¹</p> <p>Pharmacodynamics:</p> <p>Cardiovascular electrophysiology: The effect of milnacipran on the QTcF interval was measured in a double-blind, placebo and positive-controlled, parallel study in 88 healthy subjects using milnacipran 600 mg/day (3 to 6 times the recommended</p>

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therapeutic dosage for fibromyalgia). After baseline and placebo adjustment, the maximum mean QTcF change was 8 ms (2-sided 90% confidence interval, 3 to 12 ms). This increase is not considered clinically significant.¹

Pharmacokinetics:

Absorption / Distribution: Milnacipran is absorbed following oral administration with maximum concentrations (C_{max}) reached within 2 to 4 hours post dose. The absolute bioavailability is approximately 85% to 90%. The exposure to milnacipran increased proportionally within the therapeutic dose range. Steady-state levels are reached within 36 to 48 hours and can be predicted from single-dose data. The mean volume of distribution of milnacipran following a single intravenous (IV) dose to healthy subjects is approximately 400 L. Plasma protein binding is 13%.¹

Metabolism / Excretion: Milnacipran and its metabolites are eliminated primarily by renal excretion. Following oral administration of ¹⁴C-milnacipran, approximately 55% of the dose was excreted in urine as unchanged milnacipran (24% as *l*-milnacipran and 31% as *d*-milnacipran). The *l*-milnacipran carbamoyl-O-glucuronide was the major metabolite excreted in urine and accounted for approximately 17% of the dose; approximately 2% of the dose was excreted in urine as *d*-milnacipran carbamoyl-O-glucuronide. Approximately 8% of the dose was excreted in urine as the N-desethyl milnacipran metabolite. The active enantiomer, *d*-milnacipran, has a longer elimination half-life (8 to 10 hours) than the *l*-enantiomer (4 to 6 hours). There is no interconversion between the enantiomers. Milnacipran has a terminal elimination half-life of about 6 to 8 hours.¹

Clinical Studies

Study 1: Milnacipran for the Treatment of Fibromyalgia in Adults: A 15-Week, Multicenter, Randomized, Double-Blinded, Placebo-Controlled, Multiple-Dose Clinical Trial. *Funded by Forest Laboratories and Cypress Bioscience.*

This 3-month study compared total daily doses of milnacipran 100 and 200 mg with placebo. Patients were enrolled with a minimum mean baseline pain score of 40 mm or more on a 100 mm VAS ranging from 0 (“no pain”) to 100 (“worst possible pain”). The mean baseline pain score in this trial was 65. In both studies, some patients who rated themselves as globally “much” or “very much” improved experienced a decrease in pain as early as week 1 of treatment with a stable dose of milnacipran that persisted throughout these studies.¹

Conclusion: This study (1) did not use intent to treat analysis, (2) according to FDA documentation, the patient population of this study was altered after the study was completed and the initial analysis did not find significant results. A re-analysis was

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performed and reported. (3) This study had a high rate of patient discontinuation (4) there was no mention of whether or not acetaminophen, aspirin or non-steroidal anti-inflammatory were included and (5) With the number of different scales using a variety of methods for measurement, it would seem to be too complicated to get good accurate results. After a 1 to 4 week washout period, the study participants were trained in the use of an electronic diary. They then entered a 2 week baseline period, and were judged on their ability to collect the data. Those who passed were allowed to continue with the study. The rest were withdrawn.

Data collected used the following methods:

- VAS (visual analog scale)
- Patient Global Impression of Change (PGIC)
- Short-form Health Survey (SF-36)
- Physical Component Summary (PCS)
- Mental Component Summary (MCS)
- The Fibromyalgia Impact Questionnaire (FIQ)
- Medical Outcomes Study (MOS)
- Patient Global Disease Status VAS
- Multiple Ability Self-Report Questionnaire (MASQ)
- Multidimensional Health Assessment Questionnaire disability subscale
- Multidimensional Fatigue Inventory (MFI)
- Patient Global Therapeutic Benefit scale
- Arizona Sexual Experience scale

The patients in the study had to stop taking all of their other medications for fibromyalgia at least 2 weeks prior to the study. The only rescue medication allowed was hydrocodone, and it could not be used during the 2 week data collection period preceding the primary efficacy evaluation (weeks 14-15) or during the 48 hour period immediately before study visits.

Based on the data collected the patients on milnacipran showed more improvement than those patients on placebo. The percentage of responders who had a > 30% improvement from baseline morning-recall pain, and the Patient Global Impression of Change tended to be higher for milnacipran patients compared to placebo. The graphs used in the study tend to show portions of the graph so that the difference looks larger. **Milnacipran has not been compared to other drugs used to treat fibromyalgia**, therefore it may be helpful, but it is unknown if it is better than the SNRIs currently being used. Future studies are needed to directly examine the efficacy and tolerance of milnacipran when used in combination with other medications.²

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Study 2: The Efficacy and Safety of Milnacipran for the Treatment of Fibromyalgia. A Randomized, Double-blind, Placebo-controlled Trial. *Funded by Forest Laboratories and Cypress Bioscience.*

This 6-month study compared total daily doses of milnacipran 100 and 200 mg with placebo. Patients were enrolled with a minimum mean baseline pain score of 50 mm or more on a 100 mm VAS ranging from 0 (“no pain”) to 100 (“worst possible pain”). The mean baseline pain score in this trial was 69.¹

Conclusion: Study #2 is a continuation of Study #1. Similar methodology was reported as being used. The patients in the study had to stop taking all of their other medications for fibromyalgia at least 2 weeks prior to study #1. In this study they allowed the patients to take acetaminophen, aspirin or non-steroidal anti-inflammatory as needed. Hydrocodone (max of 60 mg/day) was allowed, but it could not be used during the 2 week data collection period preceding the primary efficacy evaluation (weeks 14-15 and weeks 26-27) or during the 48 hour period immediately before study visits. (1) This use of rescue medications may have interfered with the results (2) there were no details about adherence to assure that the patients received doses and (3) there were a large number of discontinued patients in this study.

Most of the people, who discontinued in the actual drug groups, did so due to adverse Events. Most people in the placebo group who discontinued did so due to Therapeutic failure. The rest of the results were consistent with Study #1.

Study #3: A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome (FMS).⁴ *Funded by: German Research Network on Neuropathic Pain*

This was a review of 26 eligible clinical studies with 2,667 evaluable patients. The objective was to systematically review the efficacy of the treatment of fibromyalgia with antidepressants.

Conclusion: (1) amitriptyline 25-50 mg/day reduces pain, fatigue and depressiveness in patients with FMS and improves sleep and quality of life. (2) Most SSRIs and the SNRIs duloxetine and milnacipran are probably also effective.

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PRICE +/-

	Usual Dose Prices listed are quoted from www.drugstore.com as of 08-24-2009	Acquisition cost
Savella (milnacipran) Titration Pack (12.5 mg #5, 25 mg #8, 50 mg #42) 28 day supply	\$109.98 per Titration Pack (\$3.90 per day)	\$\$\$\$\$ per Titration Pack (\$\$\$\$ per day)
Savella (milnacipran) 12.5 mg	\$1.99 per tablet (\$3.99 per day)	\$\$ per tablet (\$\$\$\$ per day)
Savella (milnacipran) 25 mg	Price not available	\$\$ per tablet (\$\$\$\$ per day)
Savella (milnacipran) 50 mg	\$1.99 per tablet (\$3.99 per day)	\$\$ per tablet (\$\$\$\$ per day)
Savella (milnacipran) 100 mg	\$1.89 per tablet (\$3.78 per day)	\$\$ per tablet (\$\$\$\$ per day)
<i>Cymbalta 20 mg</i>	<i>\$4.03 per capsule</i>	<i>\$\$\$ per capsule</i>
<i>Cymbalta 30 mg</i>	<i>\$4.34 per capsule</i>	<i>\$\$\$ per capsule</i>
<i>Cymbalta 60 mg</i>	<i>\$4.37 per capsule</i>	<i>\$\$\$ per capsule</i>

SIMPLICITY —

Directions for use:

The recommended dose of milnacipran is 50 mg twice daily. Maximum dosage of 100 mg twice daily.

Initial Dose Titration:

Day 1 : 12.5 mg once

Day 2-3: 12.5 mg twice daily

Day 4-7: 25 mg twice daily

After Day 7: 50 mg twice daily.

Effect of food: Absorption of milnacipran is not affected by food.

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Pharmacology/Pharmacokinetics of pregabalin (Lyrica), gabapentin (Neurontin), duloxetine (Cymbalta), and milnacipran (Savella)

	Milnacipran (Savella)	Duloxetine (Cymbalta) ^[8]	pregabalin (Lyrica) ^[10]	gabapentin (Neurontin)
Pharmacology	The exact mechanism of the central pain inhibitory action of milnacipran and its ability to improve the symptoms of fibromyalgia in humans are unknown, but are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.	Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS.	<p>Pregabalin binds with high affinity to the alpha₂-delta site in central nervous system tissues. Studies in animal models suggest that binding to this receptor may be responsible for the action of this drug. In vitro, pregabalin reduces calcium-dependent release of several neurotransmitters, possibly via modulation of calcium channel function.</p> <p>Pregabalin does not bind directly to GABA_A, GABAB, or benzodiazepine receptors. It has no effect on GABA uptake or degradation. In vitro, prolonged application of pregabalin did increase the rate of functional GABA transport.</p>	<p>The mechanism by which gabapentin exerts its analgesic action is unknown, but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli).</p> <p>Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify GABA_A or GABAB radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation.</p>
Time to Peak	2 to 4 hours	6 hours	1.5 hours	Not specified
Half-life	6 to 8 hours	12 hours	6 hours	5 to 7 hours
Elimination	55% unchanged in the urine 19% at the glucuronide	Primarily hepatic, including the CYP1A2 and CYP2D6 systems.	renal excretion	renal excretion
Drug/Food Interactions	Absorption of milnacipran (Savella) is not affected by food.	Food does not affect the Cmax of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%.	There are no clinically relevant interactions with food.	Food has only a slight effect on the rate and extent of absorption of gabapentin.

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	Milnacipran (Savella)	Duloxetine (Cymbalta) ^[8]	Pregabalin (Lyrica) ^[10]	gabapentin (Neurontin)
Black Box Warnings	Antidepressants increased the risk compared to 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.		None	None
Contraindications	<ul style="list-style-type: none"> - Concomitant use of monoamine oxidase inhibitors - Use in patients with uncontrolled narrow-angle glaucoma 		Known hypersensitivity to pregabalin or any of its components.	Known hypersensitivity to pregabalin or any of its components.
Serious Adverse Events	<ul style="list-style-type: none"> - Worsening of depressive symptoms and suicide risk - Serotonin Syndrome - Elevated blood pressure and heart rate - Seizures - Hepatotoxicity - Discontinuation symptoms - Increase in the risk of bleeding events - Higher rates of genitourinary adverse events in male patients with a history of obstructive uropathies. 	<ul style="list-style-type: none"> - Worsening of depressive symptoms and suicide risk - Hepatotoxicity - Orthostatic Hypotension and Syncope - Serotonin Syndrome - Abnormal Bleeding - Discontinuation symptoms - Activation of Mania/Hypomania - Seizures 	<ul style="list-style-type: none"> - Antiepileptic drugs, including pregabalin, increase the risk of suicidal thoughts or behavior. - Anaphylaxis - Angioedema (e.g. swelling of the throat, head and neck). - Increased seizure frequency may occur in patients with seizure disorders with rapid discontinuation. - Congestive heart failure - Peripheral edema - Vertigo - Somnolence - Dizziness - Skin ulcer - Hematemesis - Colitis. 	<ul style="list-style-type: none"> - Antiepileptic drugs, including gabapentin, increase the risk of suicidal thoughts or behavior. - Neuropsychiatric Adverse Events— Pediatric Patients 3-12 years of age. - Withdrawal Precipitated Seizure, Status Epilepticus - Tumorigenic Potential - Sudden and Unexplained Death in Patients With Epilepsy
Drug Interactions	<ul style="list-style-type: none"> - Lithium: - Epinephrine and norepinephrine - Serotonergic Drugs - Digoxin - Clonidine - Clomipramine - CNS-active drugs - Monoamine Oxidase Inhibitors (MAOIs) 	<ul style="list-style-type: none"> - Inhibitors of CYP1A2 - Inhibitors of CYP2D6 - Drugs that Interfere with hemostasis (e.g., NSAIDs, Aspirin, and Warfarin) - Drugs that Affect Gastric Acidity - Drugs Metabolized by CYP2D6 - Monoamine Oxidase Inhibitors - Serotonergic Drugs - Triptans - CNS Drugs - Drugs Highly Bound to Plasma Protein 	<p>There are currently no known drug interactions of clinical significance. Pregabalin does not undergo hepatic metabolism to any great extent (< 2%) and does not bind to plasma proteins.</p> <p>Additive effects on cognitive and motor functioning may occur when pregabalin is coadministered with CNS depressants such as narcotics, benzodiazepines, and ethanol.</p>	<ul style="list-style-type: none"> - Antacid (Maalox®) - No other significant drug-drug interactions were noted.
Cost Comparison	\$\$\$\$	\$\$\$\$\$	\$\$\$	\$

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Drug Category	Drug	FDA Approved for Fibromyalgia	Usual Therapeutic Dose/Day	Daily cost of Therapy (www.drugstore.com as of 8-25-09)	Additional Information
anticonvulsant ($\alpha_2\delta$ ligand)	Gabapentin		300-1800 mg	\$0.87 - \$3.00	
	Pregabalin (Lyrica)	Yes*	300- 450 mg	\$2.39 - \$4.70	
Tricyclics-Tertiary Amines	Amitriptyline (Elavil)		10-150 mg	\$0.13 - \$0.24	
Tricyclics-Secondary Amines	Desipramine		10-300 mg	\$0.80 - \$6.66	
	Imipramine		10-200 mg	\$0.22 - \$1.56	
Centrally Acting Muscle Relaxants	Cyclobenzaprine		10-40 mg	\$0.21 - \$0.84	
SSRIs	Fluoxetine		20- 80 mg	\$0.56 - \$2.24	
	Paroxetine (Paxil)		10 – 60 mg	\$0.16 - \$0.96	
SNRIs	Venlafaxine (Effexor)		150-225 mg	\$4.37 - \$8.36	Effexor XR going generic in 2010
	Desvenlafaxine (Pristiq)		50 mg	\$4.00	Has not been studied for use in Fibromyalgia
	Duloxetine (Cymbalta)	Yes*	30-60 mg	\$4.35	
	Milnacipran (Savella)	Yes*	100 -200 mg	\$3.78 - \$3.99	
Analgesics	Tramadol With or without acetaminophen		50-400 mg	\$0.53 - \$4.24	

* FDA approval based on studies comparing study drug to placebo. No head to head studies with other fibromyalgia medications.

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