**MILNACIPRAN**

**THERAPEUTICS**

**Brands**
- Toledomin
- Ixel
- Savella

*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: serotonin, norepinephrine reuptake inhibitor (SN-RI)
- SNRI (dual serotonin and norepinephrine reuptake inhibitor); antidepressant; chronic pain treatment

**Commonly Prescribed for**
(bold for FDA approved)
- Fibromyalgia
- Major depressive disorder
- Neuropathic pain/chronic pain

**How the Drug Works**
- Boosts neurotransmitters serotonin, norepinephrine/noradrenaline, and dopamine
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- *Weak noncompetitive NMDA-receptor antagonist (high doses), which may contribute to actions in chronic pain*
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, milnacipran can increase dopamine neurotransmission in this part of the brain

**How Long Until It Works**
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of symptoms in depression

**If It Works**
- The goal of treatment of depression is complete remission of current symptoms as well as prevention of future relapses
- The goal of treatment of fibromyalgia and chronic neuropathic pain is to reduce symptoms as much as possible, especially in combination with other treatments
- Treatment of depression most often reduces or even eliminates symptoms, but is not a cure since symptoms can recur after medicine stopped
- Treatment of fibromyalgia and chronic neuropathic pain may reduce symptoms, but rarely eliminates them completely, and is not a cure since symptoms can recur after medicine is stopped
- Continue treatment of depression until all symptoms are gone (remission)
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite
- Use in fibromyalgia and chronic neuropathic pain may also need to be indefinite, but long-term treatment is not well studied in these conditions

**If It Doesn’t Work**
- Many depressed patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some depressed patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and switch to a mood stabilizer
**Notable Side Effects**
- Most side effects increase with higher doses, at least transiently
- Headache, nervousness, insomnia, sedation
- Nausea, diarrhea, decreased appetite
- Sexual dysfunction (abnormal ejaculation/erection, impotence)
- Asthenia, sweating
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)
- Dose-dependent increased blood pressure
- Dry mouth, constipation
- Dysuria, urological complaints, urinary hesitancy, urinary retention
- Increase in heart rate
- Palpitations

**Life-Threatening or Dangerous Side Effects**
- Rare induction of mania
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)
- Rare seizures

**Weight Gain**
- Reported but not expected

**Sedation**
- Occurs in significant minority

**What to Do About Side Effects**
- Wait
- Wait
- Wait
- Lower the dose
- In a few weeks, switch or add other drugs

**Best Augmenting Agents for Side Effects**
- For urinary hesitancy, give an alpha 1 blocker such as tamsulosin or naftopidil
- Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
- Trazodone or a hypnotic for insomnia
Nevertheless, some patients respond better to higher doses (200–300 mg/day) than to lower doses. Different doses in different countries, different doses in different indications and different populations. Preferred dose for depression may be 50 mg twice daily to 100 mg twice daily in France. Preferred dose for depression in the elderly may be 15 mg twice daily to 25 mg twice daily in Japan. Preferred dosing for depression in other adults may be 25 mg twice daily to 50 mg twice daily in Japan.

Thus, clinicians must be aware that titration of twice daily dosing across a 10-fold range (30 mg–300 mg total daily dose) can optimize milnacipran’s efficacy in broad clinical use. Patients with agitation or anxiety may require slower titration to optimize tolerability. No pharmacokinetic drug interactions (not an inhibitor of CYP450 2D6 or 3A4). As milnacipran is a more potent norepinephrine reuptake inhibitor than a serotonin reuptake inhibitor, some patients may require dosing at the higher end of the dosing range to obtain robust dual SNRI actions. At high doses, NMDA glutamate antagonist actions may be a factor.

**Overdose**
- Vomiting, hypertension, sedation, tachycardia
- The emetic effect of high doses of milnacipran may reduce the risk of serious adverse effects.

**Long-Term Use**
- Safe

**Habit Forming**
- No

**How to Stop**
- Taper is prudent, but usually not necessary.

**Pharmacokinetics**
- Half-life 8 hours
- No active metabolite

**DOSING AND USE**

**Usual Dosage Range**
- 30–200 mg/day in 2 doses

**Dosage Forms**
- Capsule 25 mg, 50 mg (France, other European countries, and worldwide markets)
- Capsule 15 mg, 25 mg, 50 mg (Japan)
- Tablet 12.5 mg, 25 mg, 50 mg, 100 mg

**How to Dose**
- Should be administered in 2 divided doses
- Initial 12.5 mg once daily; increase to 25 mg/day in 2 divided doses on day 2; increase to 50 mg/day in 2 divided doses on day 4; increase to 100 mg/day in 2 divided doses on day 7; maximum dose generally 200 mg/day

**Dosing Tips**
- Preferred dose for fibromyalgia may be 100 mg twice daily
- Higher doses usually well tolerated in fibromyalgia patients
- Once daily dosing has far less consistent efficacy, so only give as twice daily
- Higher doses (>200 mg/day) not consistently effective in all studies of depression

- Bupropion, sildenafil, vardenafil, or tadalafl for sexual dysfunction
- Benzodiazepines for anxiety, agitation
- Mirtazapine for insomnia, agitation, and gastrointestinal side effects
- Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
- Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
- Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of milnacipran

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**Drug Interactions**

- Tramadol increases the risk of seizures in patients taking an antidepressant
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing milnacipran
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- Switching from or addition of other norepinephrine reuptake inhibitors should be done with caution, as the additive pro-noradrenergic effects may enhance therapeutic actions in depression, but also enhance noradrenergically mediated side effects
- Few known adverse pharmacokinetic drug interactions

**Other Warnings/Precautions**

- Use with caution in patients with history of seizures
- Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
- Can cause mild elevations in ALT/AST, so avoid use with alcohol or in cases of chronic liver disease
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
- Distribute the brochures provided by the FDA and the drug companies
- Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

**Do Not Use**

- If patient has uncontrolled angle-closure glaucoma
- If patient is taking an MAOI
- If there is a proven allergy to milnacipran

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**SPECIAL POPULATIONS**

### Renal Impairment

- Use caution for severe impairment
- For severe impairment, 50 mg/day; can increase to 100 mg/day if needed
- Not recommended for patients with end-stage renal disease

### Hepatic Impairment

- No dose adjustment necessary
- Not recommended for us in chronic liver disease

### Cardiac Impairment

- Drug should be used with caution

### Elderly

- Some patients may tolerate lower doses better
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

### Children and Adolescents

- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Not well studied

### Pregnancy

- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLTR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
**Potential Advantages**
- Fibromyalgia, chronic pain syndrome
- Patients with retarded depression
- Patients with hypersomnia

**Potential Disadvantages**
- Patients with atypical depression
- Patients with depression may have higher remission rates on SNRIs than on SSRIs
- Depressed patients with somatic symptoms, fatigue, and pain

**Primary Target Symptoms**
- Pain
- Physical symptoms
- Depressed mood
- Energy, motivation, and interest
- Sleep disturbance

**Breast Feeding**
- Some drug is found in mother’s breast milk
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reintroduced late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**
- Fibromyalgia, chronic pain syndrome
- Patients with retarded depression
- Patients with hypersomnia
in patients at higher risk, such as elderly men with borderline urine flow
• May be better tolerated than tricyclic or tetracyclic antidepressants in the treatment of fibromyalgia or other chronic pain syndromes

• No pharmacokinetic interactions or elevations in plasma drug levels of tricyclic or tetracyclic antidepressants when adding or switching to or from milnacipran

Suggested Reading


