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Medication Policy Manual

Policy No: dru175

Topic: Savella™, milnacipran

Date of Origin: April 7, 2009

Revised/Effective Date: May 8, 2009

Next Review Date: May 2010

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Milnacipran (Savella™) is a selective norepinephrine/serotonin reuptake inhibitor (SNRI) used to manage patients with fibromyalgia. Outside the US, milnacipran has been used for many years to help manage patients with depression.

Note: Though approved for marketing by the FDA, milnacipran (Savella) is not yet available in pharmacies.

Policy/Criteria

- I. Most contracts require prior authorization approval of milnacipran prior to coverage. Milnacipran may be considered medically necessary when at least two generic medications (listed in Appendix 1) have been ineffective, not tolerated, or contraindicated.

- II. Administration, Quantity Limitations, and Authorization Period
 - A. Regence considers milnacipran to be a self-administered medication.
 - B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

Position Statement

Overview

- Current national fibromyalgia treatment guidelines include the following recommendations:^[4]
 - * Non-drug therapies such as exercise and cognitive behavioral therapy are recommended as a foundation of treatment.
 - * Tricyclic antidepressants (TCAs) (e.g., amitriptyline, desipramine) or cyclobenzaprine are considered first-line medication options, and provide the best value for patients.
 - * Serotonin reuptake inhibitors (e.g., fluoxetine) or tramadol (with or without acetaminophen) may also be used with or without TCAs or cyclobenzaprine.

- Currently, pregabalin (Lyrica[®]), duloxetine (Cymbalta[®]) and milnacipran (Savella[®]) have FDA marketing approval for use in patients with fibromyalgia.^[1-3]
 - * The studies that evaluated pregabalin, duloxetine, and milnacipran in fibromyalgia compared each to placebo (inactive tablet).^[1-3]
 - * There are no studies that show that pregabalin, duloxetine, or milnacipran work any better than other medications that have been used for years to treat fibromyalgia (such as amitriptyline, cyclobenzaprine, or gabapentin). Pregabalin, duloxetine, and milnacipran are more costly than generics.

- * The effectiveness in treating fibromyalgia for all of these medications decrease over time.^[1-3]
- The unlabeled use of the following therapies is supported by randomized controlled trials and several guidelines on the management of fibromyalgia (Goldenberg DL, et al. JAMA 2004; Buckhardt CS, et al. American Pain Society 2005):^[4,8,9]
 - * Medications: amitriptyline, cyclobenzaprine, and gabapentin.
 - * Non-medication therapies: aerobic exercise, muscle strengthening, patient education, and cognitive behavior therapy.
- Similar to duloxetine, pregabalin and milnacipran, these medications (amitriptyline, cyclobenzaprine, and gabapentin) provide modest benefit to some patients with fibromyalgia pain.
- There have been no clinical trials conducted that directly compare the newer medications for fibromyalgia (duloxetine, pregabalin and milnacipran) to the older, more established medications (amitriptyline, cyclobenzaprine, and gabapentin).
- Studies evaluating the effectiveness of the older medications (amitriptyline, cyclobenzaprine, and gabapentin) have flaws similar to the studies evaluating the effectiveness of the newer medications (duloxetine, pregabalin and milnacipran).
- A recent study funded by the National Institutes of Health found that gabapentin (Neurontin) given in doses of 1,200 mg/day to 2,400 mg/day over 12 weeks decreased pain in patients with fibromyalgia better than placebo in 1 patient out of 5, a rate similar to that observed with duloxetine in other trials.^[9, 1-3]
 - * However, this study had flaws that were similar to flaws found in the studies of duloxetine, milnacipran and pregabalin in patients with fibromyalgia.

Clinical Efficacy

FIBROMYALGIA

- The studies that evaluated milnacipran in fibromyalgia compared it to placebo. There is no information that shows how well milnacipran works relative to standard therapies such as amitriptyline, cyclobenzaprine, or gabapentin for the management of patients with fibromyalgia.
- The efficacy of milnacipran in patients with fibromyalgia (without major depressive disorder) has been studied in two large, randomized, controlled trials.^[5-7]
 - * Irregularities in the design and conduct of the trials with milnacipran make the reliability of these results uncertain.^[7]
 - The specifics of the primary endpoint were changed during the trial.
 - The patient populations were altered during the trial.
 - The chosen primary endpoint differs from previous trials, making comparisons difficult.
 - * Unlike previous medication trials in fibromyalgia, the primary measure of efficacy (primary endpoint) in the milnacipran trials was the percentage of patients who achieved a combination (composite) of 3 criteria (composite syndrome responders):^[5-7]
 - At least a 30% improvement in self-reported pain.
 - A rating of “very much improved” or “much improved” on the Patient Global Impression of Change scoring survey.
 - At least a 6 point improvement on a standardized assessment of physical function (SF-36 PCS score).
 - * Overall, about 1 out of every 13 to 20 patients will achieve “composite syndrome response” (defined above) when treated with milnacipran 100 mg or 200 mg daily, as compared to treatment with a placebo.^[5-7]
 - * About 1 out of every 12 to 15 patients will experience at least a 30% improvement in pain when treated with milnacipran 100 mg or 200 mg daily, as compared to treatment with placebo.^[5-7]

DEPRESSION

- Milnacipran has been used to treat patients with major depression outside the United State for many years.^[7]
- Published trials have demonstrated that milnacipran is generally as effective as other antidepressants for management of patients with depression. There is no evidence that it is more effective than other available agents.^[10-13,]
- SSRIs, SNRIs and other antidepressants such as bupropion and mirtazapine have been proven to help relieve the symptoms of depression in 55 – 70% of people who take them.
- There is no reliable evidence that any one antidepressant (including isomers and active metabolites) is generally more effective than other available antidepressant medications at comparable doses.^[16-22]

Multiple systematic reviews and meta-analyses have been published.[ref] Generally these reviews have concluded that there are no significant overall differences in safety or efficacy between second-generation antidepressants in the management of major depressive disorder.^[16-21]

- * One meta-analysis concluded that sertraline and escitalopram may have advantages in efficacy and safety, but these results will need to be confirmed.^[22]
- “The Sequenced Treatment Alternatives to Relieve Depression (STARSTAR*D) trial was designed to evaluate the value of switching to another antidepressant or augmenting with another antidepressant after initial unsuccessful treatment with an SSRI (citalopram).^[14,15]
 - * Approximately one in four patients experienced a remission of symptoms after switching to another antidepressant, though there was no advantage of one agent over another.^[14]
 - * Augmentation of citalopram with either bupropion SR or buspirone both resulted in an additional 30% of patients achieving remission.^[15]
 - * The STARSTAR*D trial was not designed to evaluate the superiority of any particular medication over another. In addition, problems with trial design add uncertainty to the trial’s conclusions. This study should be used with caution.

Safety

- The FDA states that the safety profile of milnacipran HCl (Savella) appears to be similar to the class of SNRI antidepressants. ^[1,7]
- The most common adverse events occurring in Savella-treated subjects in the placebo-controlled fibromyalgia trials were: nausea, headache, constipation, insomnia, hot flush and dizziness. ^[1,7]
- Discontinuations due to adverse events from the two Phase 3 trials occurred most frequently in the Savella 200-mg/day group (24%), followed by the Savella 100-mg/day group (19%), and then the placebo group (9%). ^[5-7]
- Cardiovascular adverse events (such as hypertension, tachycardia, and palpitations) were a concern during the clinical development program. Milnacipran HCl (Savella) carries a warning to monitor for cardiovascular adverse events and to discontinue the drug if they occur. ^[5-7]
 - * Adverse events most frequently associated with discontinuation were nausea, palpitations, depression, increased heart rate, constipation, headache, insomnia, hyperhidrosis, vomiting, dizziness and fatigue. ^[5-7]

References

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Appendix 1: Generic Medication Alternatives

Condition	Generic Alternatives
Mental Health Conditions including, but not limited to: - major depression - social anxiety disorder - generalized anxiety disorder - panic disorder - bulimia - post-traumatic stress disorder - premenstrual dysphoric disorder	- citalopram (Celexa [®]) - fluoxetine (Prozac [®]) - fluvoxamine (Luvox [®]) - paroxetine (Paxil [®]) sertraline (Zoloft [®]) - bupropion SR/XL (Wellbutrin SR [®] , Wellbutrin XL [®] 300mg) - mirtazapine (Remeron [®]) - venlafaxine (Effexor [®]) - venlafaxine SR tablets
Neuropathic Pain	- gabapentin (Neurontin [®]) - tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline)
Fibromyalgia	- gabapentin (Neurontin [®]) - tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline) - cyclobenzaprine (Flexeril [®])

Cross References

Cymbalta [®] , duloxetine dru147
Lexapro [®] ; escitalopram dru148
Effexor XR [®] ; venlafaxine extended release dru146
Luvox CR [®] ; fluvoxamine extended-release capsules dru153
Pristiq [®] , desvenlafaxine dru154
Lyrica [®] , pregabalin dru122

Codes	Number	Description
N/A		