Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) Step Therapy

Policy Number: 5.01.588  Last Review: 7/2019
Origination: 7/2014  Next Review: 7/2020
LoB: ACA

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for brand name Serotonin and Norepinephrine Reuptake Inhibitors when the following criteria are met. The brand name medications affected are:

- Cymbalta® (duloxetine HCl delayed-release capsules – Lilly, generics)
- Desvenlafaxine extended-release tablets (Alembic/Ranbaxy [brand product])
- Desvenlafaxine fumarate extended-release tablets (Sun Pharma/Caraco [brand product])
- Effexor® (venlafaxine HCl tablets – Wyeth, generics)
- Effexor® XR (venlafaxine HCl extended-release capsules – Wyeth, generics)
- Fetzima® (levomilnacipran HCl extended-release capsules – Forest)
- Irinika™ (duloxetine 40 mg delayed-release capsules – Lupin, generic)
- Khedezla™ (desvenlafaxine extended-release tablets – Osmotica/Macoven)
- Pristiq® (desvenlafaxine succinate extended-release tablets – Wyeth)
- Savella® (milnacipran HCl tablets – Forest)
- Venlafaxine HCl extended-release tablets (Upstate Pharma/Osmotica [brand product], generics)

When Policy Topic is covered
This step therapy program has been developed to encourage the use of one SSRI (brand or generic) or one generic SNRI prior to the use of a Step 2 SNRI, other than Savella. In addition, this program encourages the use of two agents from Step 1 and/or Step 2 prior to the use of Savella. If the step therapy rule is not met for a Step 2 agent at the point of service, coverage will be determined by the step therapy criteria below. All approvals are provided for 1 year in duration.

Automation: Patients with a history of one Step 1 drug within the 130-day look-back period are excluded from step therapy (other than Savella). The automated component for Savella screens for two agents from Step 1 and/or Step 2. Patients > 18 years of age will be targeted in this step therapy program.

Step 1: citalopram tablets (Celexa, generic), generic citalopram oral solution, fluoxetine immediate-release capsules and tablets (Prozac, Sarafem, generic), generic fluoxetine oral solution, fluoxetine delayed-release capsules (Prozac Weekly, generics), generic fluvoxamine immediate-release tablets, generic fluvoxamine extended-release capsules (Luvox CR, generics), paroxetine HCl immediate- and controlled-release tablets (Paxil, Paxil CR, generic), paroxetine oral suspension (Paxil, generic), sertraline tablets (Zoloft, generic), sertraline oral solution (Zoloft, generic), escitalopram tablets (Lexapro, generic), escitalopram oral solution (Lexapro, generic), Pexeva, Viibryd, generic
duloxetine delayed-release capsules, generic venlafaxine immediate-release tablets, generic venlafaxine extended-release capsules, generic venlafaxine extended-release tablets

**Step 2:** Effexor, Effexor XR, Cymbalta, Pristiq, Desvenlafaxine extended-release tablets (brand product), Desvenlafaxine fumarate extended-release tablets (brand product), Venlafaxine extended-release tablets (brand product), Savella, Khedezla, Fetzima, Irenka

**Criteria**

1. If a patient has tried one Step 1 product, then authorization for a Step 2 product (other than Savella) may be given.

2. If a patient has tried at least two other agents (e.g., SSRI, SNRI, TCA, bupropion), then authorization for Savella may be given.

3. Exceptions can be made for Savella if the patient is treating fibromyalgia (with or without depression).

4. Patients who are currently taking or who have taken brand name Pristiq, Desvenlafaxine extended-release tablets, Desvenlafaxine fumarate extended-release tablets, Khedezla, or Fetzima at any time in the past and discontinued their use may receive authorization for the SNRI that they have used.

5. Exceptions can be made for Pristiq, Desvenlafaxine extended-release tablets, Desvenlafaxine fumarate extended-release tablets, Khedezla, or Fetzima if the patient has suicidal ideation.

**When Policy Topic is not covered**
The use of Serotonin and Norepinephrine Reuptake Inhibitors is considered **investigational** for all other indications.

**Considerations**
Serotonin and Norepinephrine Reuptake Inhibitors require prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

**Description of Procedure or Service**
Duloxetine, Pristiq, Fetzima, Khedezla, desvenlafaxine, and venlafaxine are serotonin and norepinephrine reuptake inhibitors (SNRIs) indicated for the treatment of depression. In addition, venlafaxine is indicated for the treatment of generalized anxiety disorder (GAD), social anxiety disorder, and panic disorder. Duloxetine delayed-release capsules are indicated for the treatment of GAD, the management of neuropathic pain associated with diabetic peripheral neuropathy, the management of fibromyalgia, and the management of chronic musculoskeletal pain. Savella is only indicated for the management of fibromyalgia. While Savella is approved outside the US for major depressive disorder (MDD), it is not in development for this or any other indication in the US.

A venlafaxine extended-release tablet formulation is also available. This formulation does not carry the same indications as the capsule formulation (Effexor XR, generics). Venlafaxine extended-release tablets are indicated for MDD and social anxiety disorder. Equal doses of venlafaxine extended-release tablets are bioequivalent to venlafaxine extended-release capsules (Effexor XR, generics) when administered under fed conditions; however, these products are not AB-rated to each other (although they do each have their own AB-rated generics). Similarly, in addition to Pristiq, branded
Desvenlafaxine and Desvenlafaxine fumarate products and Khedezla are available.\textsuperscript{4,7-9} Desvenlafaxine, Desvenlafaxine fumarate, Khedezla, and Pristiq are available in the same strength extended-release tablets, and share the same indication (treatment of MDD). Desvenlafaxine, Desvenlafaxine fumarate, Khedezla, and Pristiq are not AB-rated to each other. However, efficacy studies conducted with Pristiq are cited in the Desvenlafaxine, Desvenlafaxine fumarate, and Khedezla product information. Irenka was approved by the Food and Drug Administration (FDA) as a generic to duloxetine delayed-release capsules (Cymbalta, generics). Irenka is being marketed as a branded product and has the same indications as duloxetine delayed-release capsules with the exception of fibromyalgia.\textsuperscript{30} Lupin has also launched an authorized generic to Irenka.

The selective serotonin reuptake inhibitors (SSRIs) are a pharmacologic class of agents with antidepressant action and efficacy in the treatment of a wide range of mood and anxiety disorders that include obsessive compulsive disorder (OCD), panic disorder, social anxiety disorder (social phobia), posttraumatic stress disorder (PTSD), bulimia-nervosa, and GAD.\textsuperscript{11} There are many off-label uses of the SSRIs and SNRIs in a wide variety of psychiatric, as well as nonpsychiatric conditions. It should be kept in mind that some patients may have a primary disorder, such as depression, and a comorbid condition, such as anxiety or sleep disorder, which may or may not affect response or the ability to tolerate adverse events (AEs).

Rationale

Indications

All of the SNRIs (with the exception of Savella) are indicated for the treatment of MDD. Some of the SNRIs carry additional indications (Table 1). Table 2 provides the approved indications for the available SSRIs.

Table 1. FDA-Approved Indications for the SNRIs in Adults.\textsuperscript{1-10,30}

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>MDD</th>
<th>GAD</th>
<th>Social Anxiety Disorder</th>
<th>Panic Disorder</th>
<th>DPN Pain</th>
<th>Chronic Musculoskeletal Pain</th>
<th>Fibromyalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cymbalta\textsuperscript{®} (duloxetine delayed-release capsules, generics)</td>
<td>X</td>
<td>X\textsuperscript{*}</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Desvenlafaxine extended-release tablets (Brand product)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine fumarate extended-release tablets (Brand product)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effexor\textsuperscript{®} (venlafaxine immediate-release tablets, generics)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effexor XR\textsuperscript{®} (venlafaxine extended-release capsules, generics)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetzima\textsuperscript{™} (levomilnacipran extended-release capsules)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irenka\textsuperscript{™} (duloxetine 40 mg delayed-release capsules)</td>
<td>X</td>
<td>X\textsuperscript{*}</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khedezla\textsuperscript{™} (desvenlafaxine extended-release tablets)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pristiq\textsuperscript{®} (desvenlafaxine succinate extended-release tablets)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Savella\textsuperscript{®} (milnacipran tablets)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Venlafaxine extended-release tablets (Brand product, generics)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SNRI – Serotonin norepinephrine reuptake inhibitor; FDA – Food and Drug Administration; MDD – Major Depressive Disorder; GAD – Generalized Anxiety Disorder; DPN – Diabetic Peripheral Neuropathy; ^ Efficacy studied in patients ≥ 7 years of age with GAD.
Table 2. Food and Drug Administration (FDA)-Approved Indications for the SSRIs

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>MDD</th>
<th>OCD</th>
<th>Panic Disorder</th>
<th>Bulimia Nervosa</th>
<th>PTSD</th>
<th>Social Anxiety Disorder</th>
<th>GAD</th>
<th>PMDD</th>
<th>VMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celexa® (citalopram tablets and oral solution, generics)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levoxipro® (escitalopram tablets and oral solution, generics)</td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prozac® (fluoxetine tablets, and oral solution, generics)</td>
<td>X†</td>
<td>X†</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prozac Weekly® (fluoxetine delayed-release capsules, generics)</td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarafem® (fluoxetine capsules and tablets, generics)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine (generics only)</td>
<td>X†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luvox CR® (fluvoxamine extended-release capsules, generics)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paxil® (paroxetine HCl tablets and oral suspension, generics)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paxil CR® (paroxetine HCl controlled-release tablets, generics)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pexeva® (paroxetine mesylate tablets)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brisdelle® (paroxetine 7.5 mg capsules)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoloft® (sertraline tablets and oral suspension, generics)</td>
<td>X</td>
<td>X†</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viibryd® (vilazodone tablets)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brintellix™ (vortioxetine tablets)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SSRI – Selective serotonin reuptake inhibitor; FDA – Food and Drug Administration; MDD – Major Depressive Disorder; OCD – Obsessive compulsive disorder; PTSD – Posttraumatic stress disorder; GAD – Generalized anxiety disorder; PMDD – Premenstrual dysphoric disorder; VMS – Vasomotor symptoms; α FDA-approved indication includes adolescents 12 to 17 years of age; † FDA-approved indication includes children and adolescents; § Approved for the prevention of relapse during the continuation treatment phase of depression; CR – Controlled release; HCl – Hydrochloride.

Neuropathic Pain (not related to DPN)

None of the SSRIs or SNRIs are indicated for the management of neuropathic pain unrelated to DPN. A variety of agents have been utilized including TCAs (e.g., amitriptyline), anticonvulsants (i.e., gabapentin, carbamazepine), capsaicin, and clonidine.25-27 Regarding the use of antidepressants, the TCAs (particularly amitriptyline) appear the most efficacious, and are one of the first-line therapy options, whereas SSRIs displayed limited effects.27-28 SNRIs (venlafaxine and duloxetine) are also considered one of the first-line therapy options in treating neuropathic pain in patients with or without comorbid depression.28 Both TCAs and SNRIs demonstrate superiority over SSRIs. Consistent efficacy in neuropathic pain has been demonstrated in randomized, controlled trials for SNRIs (venlafaxine and duloxetine), as well as topical analgesics, anticonvulsants, TCAs, opioids, and baclofen. Antidepressants are a logical choice, not only because of their efficacy, but also because clinically significant depression is commonly comorbid with pain.

The Mayo Foundation recommendations for pharmacological management of neuropathic pain (2010) state that TCAs, dual reuptake inhibitors of serotonin and norepinephrine (duloxetine and venlafaxine), calcium channel ligands (gabapentin and Lyrica), and topical lidocaine are recommended as first-line treatment options.29 Opioid analgesics and tramadol are recommended as second-line treatments that can be considered first-line in certain clinical circumstances.
References

18. Pexeva® tablets [prescribing information]. Miami, FL: Noven Therapeutics LLC.; May 2014.

Other References Utilized


Billing Coding/Physician Documentation Information

N/A The Serotonin and Norepinephrine Reuptake Inhibitors are considered a pharmacy benefit.

Additional Policy Key Words

Policy Number: 5.01.588

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/2014</td>
<td>New Policy titled Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) Step Therapy Program</td>
</tr>
<tr>
<td>07/2015</td>
<td>Annual revision- no changes made</td>
</tr>
<tr>
<td>07/2016</td>
<td>Annual revision- no changes made to policy statement</td>
</tr>
<tr>
<td>07/2017</td>
<td>Annual revision- no changes made to policy statement</td>
</tr>
<tr>
<td>07/2018</td>
<td>Annual review – no changes made</td>
</tr>
<tr>
<td>07/2019</td>
<td>Annual review – no changes made</td>
</tr>
</tbody>
</table>

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.