STEP THERAPY POLICY

POLICY: Antidepressants – Serotonin and Norepinephrine Reuptake Inhibitors Step Therapy Policy

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

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OVERVIEW

Desvenlafaxine, duloxetine, Fetzima, Khedezla, and venlafaxine are serotonin and norepinephrine reuptake inhibitors (SNRIs) indicated for the **treatment of depression**.[1-10] 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.[11] 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 hydrochloride (HCl) extended-release *tablet* formulation and a venlafaxine *besylate* extended-release tablet are also available.[5,6] These formulations do not carry the same indications as the capsule formulation (Effexor XR, generic). Venlafaxine HCl extended-release tablets are indicated for MDD and social anxiety disorder.[5] Equal doses of venlafaxine HCl extended-release tablets are bioequivalent to venlafaxine extended-release *capsules* (Effexor XR, generic) when administered under fed conditions; however, these products are not AB-rated to each other. Venlafaxine besylate extended-release tablets are indicated for MDD and GAD, and they are only available in a 112.5 mg strength.[6] Venlafaxine besylate extended-release tablets cannot be used to initiate venlafaxine treatment, titrate by doses less than 112.5 mg, or taper treatment.

Similarly, in addition to desvenlafaxine succinate extended-release tablets (Pristiq, generic), branded Desvenlafaxine and Khedezla are available.[4,8-10] Desvenlafaxine, desvenlafaxine succinate, and Khedezla are available in the same strength extended-release tablets, and share the same indication (treatment of MDD). Desvenlafaxine, Desvenlafaxine fumarate (discontinued), desvenlafaxine succinate, and Khedezla are not AB-rated to each other. However, efficacy studies conducted with desvenlafaxine succinate are cited in the Desvenlafaxine and Khedezla product information. Irenka was approved by the FDA as a generic to duloxetine delayed-release capsules (Cymbalta, generic). Irenka is being marketed as a branded product and has the same indications as duloxetine delayed-release capsules with the exception of fibromyalgia.[12] Lupin has also launched an authorized generic to Irenka. Drizalma Sprinkle relied on

clinical efficacy studies for Cymbalta for approval and has the same indications as Cymbalta with the exception of a fibromyalgia indication.[1,10]

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.[13] There are many off-label uses for the SSRIs and SNRIs in a wide variety of psychiatric, as well as nonpsychiatric, conditions. Of note, 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).

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.[1-12]

Brand (generic)	MDD	GAD	SAD	Panic Disorder	DPN Pain	Chronic Musculoskeletal Pain	Fibro-myalgia
Cymbalta® (duloxetine delayed-release capsules, generic)	X	X^			X	X	X*
Desvenlafaxine extended-release tablets (Brand product)	X						
Drizalma Sprinkle™ (duloxetine delayed-release capsules)	X	X^			X	X	
Effexor® (venlafaxine immediate-release tablets, generic)	X						
Effexor XR® (venlafaxine extended-release capsules, generic)	X	X	X	X			
Fetzima™ (levomilnacipran extended-release capsules)	X						
Irenka™ (duloxetine 40 mg delayed-release capsules)	X	X^			X	X	
Khedezla™ (desvenlafaxine extended-release tablets)	X						
Pristiq® (desvenlafaxine succinate extended-release tablets, generic)	X						
Savella® (milnacipran tablets)							X
Venlafaxine HCl extended-release tablets (generic)	X		X				
Venlafaxine besylate extended-release tablets (brand product)	X	X					

SNRI – Serotonin norepinephrine reuptake inhibitor; MDD – Major depressive disorder; GAD – Generalized anxiety disorder; SAD – Social Anxiety Disorder; DPN – Diabetic peripheral neuropathy; ^ Efficacy studied in patients ≥ 7 years of age with GAD; * Approved for use in patients ≥ 13 years of age; HCl – Hydrochloride.

Table 2. FDA-Approved Indications for the SSRIs.[14-26]

Brand (generic)	MDD	OCD	Panic Disorder	Bulimia Nervosa	PTSD	SAD	GAD	PMDD	VMS
Celexa® (citalopram tablets and oral solution, generic)	X								
Lexapro® (escitalopram tablets and oral solution, generic)	Xα						X		
Prozac® (fluoxetine capsules, tablets, and oral solution, generic)	X†	X†	X	X					

Table 2 (continued). FDA-Approved Indications for the SSRIs.[14-26]

Brand (generic)	MDD	OCD	Panic Disorder	Bulimia Nervosa	PTSD	SAD	GAD	PMDD	VMS
fluoxetine delayed-release capsules (generic to Prozac® Weekly™)	X*								
Sarafem® (fluoxetine capsules and tablets, generic only)								X	
Fluvoxamine (generic only)		X†							
fluvoxamine extended-release capsules (generic only)		X†							
Paxil® (paroxetine HCl tablets and oral suspension, generic)	X	X	X		X	X	X		
Paxil CR® (paroxetine HCl controlled-release tablets, generic)	X		X			X		X	
Pexeva® (paroxetine mesylate tablets)	X	X	X				X		
Brisdelle™ (paroxetine 7.5 mg capsules)									X
Zoloft® (sertraline tablets and oral suspension, generic)	X	X†	X		X	X		X	
Viibryd® (vilazodone tablets)	X								
Trintellix™ (formerly Brintellix®) [vortioxetine tablets]	X								

SSRI – Selective serotonin reuptake inhibitor; MDD – Major depressive disorder; OCD – Obsessive compulsive disorder; PTSD – Posttraumatic stress disorder; SAD – Social Anxiety Disorder; GAD – Generalized anxiety disorder; PMDD – Premenstrual dysphoric disorder; VMS – Vasomotor symptoms; ᵅ 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.

POLICY STATEMENT

This program has been developed to encourage the use of a Step 1 Product prior to the use of a Step 2 Product (other than Savella). In addition, this program encourages the use of two Products 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 Product 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: A patient with a history of one Step 1 Product within the 130-day look-back period is excluded from Step Therapy (other than Savella). A patient with a of two Products from Step 1 and/or Step 2 within the 130-day look-back period is excluded from Step Therapy for Savella. Patients > 18 years of age are targeted in this Step Therapy program.

Step 1: citalopram tablets (Celexa, generic), generic citalopram oral solution, generic duloxetine delayed-release 20 mg, 30 mg, 60 mg capsules, escitalopram tablets (Lexapro, generic), escitalopram oral solution (Lexapro, generic), fluoxetine immediate-release capsules and tablets (Prozac, Sarafem, generic), generic fluoxetine oral solution, generic fluoxetine delayed-release capsules, generic fluvoxamine immediate-release tablets, generic fluvoxamine extended-release capsules, paroxetine HCl immediate- and controlled-release tablets (Paxil, Paxil CR, generic), paroxetine oral suspension (Paxil, generic), Pexeva, sertraline tablets (Zoloft, generic), sertraline oral solution (Zoloft, generic), Trintellix (formerly Brintellix), Viibryd, generic venlafaxine immediate-release tablets, generic venlafaxine extended-release capsules

Step 2: Cymbalta, Desvenlafaxine extended-release tablets (brand product), Drizalma Sprinkle, Effexor, Effexor XR, Fetzima, Irenka, Khedezla, Pristiq, Savella, generic desvenlafaxine

succinate extended-release tablets, generic duloxetine 40 mg delayed-release capsules, generic venlafaxine extended-release tablets, venlafaxine besylate extended-release tablets

CRITERIA

1. If the patient has tried one Step 1 Product, approve a Step 2 Product (other than Savella).

2. If the patient has tried at least two Products from Step 1 and/or Step 2 (other than Savella), approve Savella.

3. If the patient is being treated for fibromyalgia (with or without depression) and the patient has tried duloxetine delayed-release capsules (brand or generic), approve Savella.

4. If the patient is currently taking or has taken brand name Desvenlafaxine extended-release tablets, desvenlafaxine succinate extended-release tablets (Pristiq or generics), Khedezla, or Fetzima at any time in the past and discontinued its use, approve the Product that they have used.

5. If the patient has suicidal ideation, approve Desvenlafaxine extended-release tablets, desvenlafaxine succinate extended-release tablets (Pristiq or generics), Khedezla, or Fetzima.

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