STEP THERAPY POLICY

POLICY: Antidepressants Step Therapy Policy

Medications	Manufacturer	Generic Availability
Bupropion Medications		
Aplenzin® (bupropion hydrobromide extended-release tablets)	Bausch Health	
Auvelity® (dextromethorphan hydrobromide and bupropion hydrochloride extended-release tablets)	Axsome	
Bupropion XL tablets (brand products, authorized generic to Forfivo XL)	various	
Exxua (gepirone extended-release tablets)	Fabre Kramer	
Forfivo XL (bupropion hydrochloride extended-release tablets)	Almatica	
Wellbutrin SR® (bupropion hydrochloride sustained-release tablets)	GlaxoSmithKline	X
Wellbutrin XL® (bupropion hydrochloride extended-release tablets)	Bausch Health	X
Selective Serotonin Reuptake Inhibitor Medications		
Celexa® (citalopram tablets and oral solution)	AbbVie	X
Citalopram capsules (brand product)	Almatica	
Escitalopram capsules (brand product)	Almatica	
Fluoxetine capsules (generic to discontinued Sarafem® capsules)		X
Fluoxetine delayed-release capsules (generic to discontinued Prozac® Weekly™)		X
Fluoxetine tablets (generic only)		X
Fluvoxamine extended-release capsules (generic only)		X
Fluvoxamine tablets (generic only)		X
Lexapro® (escitalopram tablets and oral solution)	AbbVie	X
Paroxetine mesylate 7.5 mg capsules (generic to discontinued Brisdelle®)		X
Paxil® (paroxetine hydrochloride tablets and oral suspension)	Apotex	X
Paxil CR® (paroxetine hydrochloride controlled-release tablets)	Apotex	X
Pexeva® (paroxetine mesylate tablets) [discontinued 5/2023]	Sebela	
Prozac® (fluoxetine capsules, tablets, and oral solution)	Lilly	X
Sertraline capsules	Almatica/Viking	X
Trintellix® (vortioxetine tablets)	Takeda	
Viibryd® (vilazodone hydrochloride tablets)	AbbVie	X
Zoloft® (sertraline tablets and oral solution)	Viatris	X
Serotonin and Norepinephrine Reuptake Inhibitor Medications		
Cymbalta® (duloxetine delayed-release capsules)	Lilly	X
Desvenlafaxine extended-release tablets (brand product)	Alembic /Ranbaxy	
Drizalma Sprinkle™ (duloxetine delayed-release capsules)	Sun	
Effexor XR® (venlafaxine extended-release capsules)	Wyeth	X
Fetzima™ (levomilnacipran extended-release capsules)	Forest	
Pristiq® (desvenlafaxine succinate extended-release tablets)	Wyeth	X
Savella® (milnacipran tablets)	Forest	
Venlafaxine besylate extended-release tablets (brand product)	Almatica	
Venlafaxine HCl immediate-release tablets (generic only)		X
Venlafaxine HCl extended-release tablets (generic only)		X

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INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna National Formulary Coverage:

OVERVIEW

Bupropion Products

Aplenzin, Auvelity, Exxua, Forfivo XL (authorized generics), bupropion hydrochloride (HCl) sustained-release (SR) tablets, and bupropion HCl extended-release (ER) tablets are indicated for the **treatment of depression**.[1-6] Bupropion HCl ER tablets and Aplenzin are also indicated for the prevention of seasonal major depressive episodes in patients with seasonal affective disorder.[2,3] Table 1 lists the available bupropion-containing products.

Table 1. Available Long-Acting Bupropion-Containing Products.[1-6]

Brand / Generic name	Formulation	Strengths	Notes
Aplenzin® (bupropion HBr)	ER tablets	174, 348, 522 mg	Strengths are equivalent to 150, 300, and 450 mg of bupropion HCl, respectively.
Auvelity™ (dextromethorphan HBr and bupropion HCl)	ER tablets	45 mg/105 mg	Bupropion increases plasma levels of dextromethorphan by competitively inhibiting CYP2D6, which catalyzes a major biotransformation pathway for dextromethorphan.
Exxua (gepirone)	ER tablets	18.2, 36.3, 54.5, and 72.6 mg	Correct electrolyte abnormalities and perform ECG prior to initiating and during treatment; do not initiate therapy if QTc is > 450 msec.

Forfivo XL (bupropion HCl), authorized generics	ER tablets	450 mg	Use another bupropion formulation for initial dose titration. Patients being treated with other bupropion products at 450 mg/day can be switched to equivalent dose of Forfivo XL once daily.
Wellbutrin SR® (bupropion HCl), generic	SR tablets	100, 150, 200 mg	Available generically.
Wellbutrin XL® (bupropion HCl), generic	ER tablets	150, 300 mg	Available generically.

HBr – Hydrobromide; HCl – Hydrochloride; ER – Extended-release; CYP – Cytochrome P450; SR – Sustained-release.

Aplenzin contains bupropion hydrobromide (HBr). Of note, 174 mg/day of bupropion HBr is equivalent to 150 mg/day of bupropion HCl.[3] Therefore, when switching patients from bupropion HCl SR or ER tablets to Aplenzin (or vice versa), it is possible to give equivalent daily doses. Aplenzin is bioequivalent to bupropion HCl ER tablets, which has been demonstrated to have similar bioavailability to both the immediate-release and the SR formulations of bupropion. Forfivo XL (authorized generics) is available as 450 mg ER tablets, while the other bupropion HCl ER tablets are available as 150 mg or 300 mg.[2,4]

Auvelity contains a combination of dextromethorphan HBr, an uncompetitive N-methyl D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist, and bupropion HCl, an aminoketone and cytochrome P450 (CYP)2D6 inhibitor.[5] Each tablet contains 45 mg dextromethorphan HBr (equivalent to 32.98 mg dextromethorphan base) in an immediate-release formulation and 105 mg bupropion HCl (equivalent to 91.14 mg bupropion base) in an ER formulation.

Exxua is an analog of buspirone. The mechanism of the antidepressant effect is not fully understood but it is thought to be related to its modulation of serotonergic activity in the central nervous system through selective agonist activity at 5HT1A receptors.[6]

Zyban® (bupropion HCl SR, generic only) contains the same active ingredient as bupropion HCl SR and ER tablets and Forfivo XL (authorized generics); however, Zyban is indicated as an aid to smoking cessation treatment.[7] Because of the different indication for use, Zyban is not included in this policy.

Selective Serotonin Reuptake Inhibitor (SSRI) Products

The SSRIs comprise a pharmacologic class of agents with antidepressant action and efficacy in the treatment of a wide range of mood and anxiety disorders (see Table 2).[8-23]

Table 2. FDA-Approved Indications for the SSRIs.[8-23]

Brand (generic)	MDD	OCD	Panic Disorder	Bulimia Nervosa	PTSD	SAD	GAD	PMDD	VMS
Celexa® (citalopram tablets and oral solution, generic) and citalopram capsules	X								
Escitalopram capsules	X#						X#		
Fluoxetine delayed-release capsules (generic to Prozac® Weekly™)	X*								
Fluoxetine capsules and tablets (generic to Sarafem®)								X	
Fluvoxamine extended-release capsules (generic only)		X†				X			
Fluvoxamine (generic only)		X†							
Lexapro® (escitalopram tablets and oral solution, generic)	Xα						X^		
Paroxetine mesylate 7.5 mg capsules (generic to Brisdelle®)									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		
Prozac® (fluoxetine capsules, tablets, and oral solution, generic)	X†	X†	X	X					
Sertraline capsules	X	X†							
Trintellix™ (vortioxetine tablets)	X								
Viibryd® (vilazodone tablets, generic)	X								
Zoloft® (sertraline tablets and oral suspension, generic)	X	X†	X		X	X		X	

SSRIs – Selective serotonin reuptake inhibitors; 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; # Approved in adults < 65 years of age; * Approved for the prevention of relapse during the continuation treatment phase of depression; † FDA-approved indication includes children and adolescents; α FDA-approved indication includes adolescents 12 to 17 years of age; ^ FDA-approved indication includes children and adolescents 7 to 17 years of age; CR – Controlled release; HCl – Hydrochloride.

Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) Products

Desvenlafaxine, duloxetine, Fetzima, and venlafaxine are SNRIs indicated for the **treatment of depression**.[24-33] Additional indications vary by product. Table 3 provides the approved indications for the available SSRIs. While Savella is approved outside the US for major depressive disorder (MDD), it is not in development for this indication in the US.

A venlafaxine *hydrochloride* (HCl) extended-release tablet formulation and a venlafaxine *besylate* extended-release tablet are also available.[28,29] 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.[28] 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.[29] 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 is available.[27,31] Desvenlafaxine and desvenlafaxine succinate are available in the same strength extended-release tablets, and share the same indication (treatment of MDD). Desvenlafaxine, Desvenlafaxine fumarate (discontinued), and desvenlafaxine succinate are not AB-rated to each other. However, efficacy studies conducted with desvenlafaxine succinate are cited in the Desvenlafaxine product information. 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.[24,32]

Table 3. FDA-Approved Indications for the SNRIs in Adults.[24-33]

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 XR® (venlafaxine extended-release capsules, generic)	X	X	X	X			
Fetzima™ (levomilnacipran extended-release capsules)	X						
Pristiq® (desvenlafaxine succinate extended-release tablets, generic)	X						
Savella® (milnacipran tablets)							X
Venlafaxine besylate extended-release tablets (brand product)	X	X					
Venlafaxine HCl immediate-release tablets (generic only)	X						
Venlafaxine HCl extended-release tablets (generic)	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.

POLICY STATEMENT

This program has been developed to encourage the use of one Step 1 Product (Standard Criteria) or two Step 1 Products (High Impact Criteria) prior to the use of a Step 2 Product in adults. 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.

Step 1: generic bupropion extended-release tablets, generic bupropion sustained-release tablets, generic citalopram oral solution, generic citalopram tablets, generic duloxetine delayed-release (20 mg, 30 mg, 60 mg) capsules, generic escitalopram tablets, generic fluoxetine immediate-release capsules, generic fluoxetine oral solution, generic fluvoxamine immediate-release tablets, generic paroxetine HCl immediate-release tablets, generic sertraline oral solution, generic sertraline tablets, generic venlafaxine extended-release capsules, generic venlafaxine immediate-release tablets

Step 2: Aplenzin, Auvelity, Bupropion XL tablets (authorized generics to Forfivo XL), Celexa, Citalopram capsules (brand), Cymbalta, Desvenlafaxine extended-release tablets (brand), generic desvenlafaxine succinate extended-release tablets, generic duloxetine 40 mg delayed-release capsules, Drizalma Sprinkle, Effexor XR, Escitalopram capsules (brand), generic escitalopram oral solution, Exxua, Fetzima, generic fluoxetine delayed-release 90 mg capsule, generic fluoxetine immediate-release tablets, generic fluvoxamine extended-release capsules, Forfivo XL, Lexapro, Paxil, Paxil CR, generic paroxetine HCl controlled-release (CR)/extended-release (ER) tablets, generic paroxetine HCl oral suspension, generic paroxetine mesylate capsules, Pexeva, Pristiq, Prozac, Sarafem, Savella, sertraline capsules, Trintellix, Venlafaxine besylate extended-release tablets (brand), generic venlafaxine HCl extended-release tablets, generic vilazodone hydrochloride tablets, Viibryd, Wellbutrin SR, Wellbutrin XL, Zoloft

Antidepressants Step Therapy Policy **product(s) is(are) covered as medically necessary when the following step therapy criteria is(are) met. Any other exception is considered not medically necessary.**

STANDARD CRITERIA

1. If the patient has tried one Step 1 Product, approve a Step 2 Product.

2. If the patient is currently taking or has taken Desvenlafaxine extended-release tablets (brand product), desvenlafaxine succinate extended-release tablets (Pristiq or generics), Exxua, Fetzima, Pexeva, vilazodone hydrochloride tablets (Viibryd or generics), or Trintellix at any time in the past and discontinued its use, approve the Product that they have used.

3. If the patient cannot swallow or has difficulty swallowing tablets or capsules, approve generic escitalopram oral solution or generic paroxetine HCl oral suspension.

4. If the patient has suicidal ideation, approve Desvenlafaxine extended-release tablets (brand product), desvenlafaxine succinate extended-release tablets (Pristiq or generics), Exxua, Fetzima, Pexeva, vilazodone hydrochloride tablets (Viibryd or generics), or Trintellix.

HIGH IMPACT CRITERIA

1. If the patient has tried two Step 1 Products, approve a Step 2 Product.

2. If the patient is currently taking or has taken Desvenlafaxine extended-release tablets (brand product), desvenlafaxine succinate extended-release tablets (Pristiq or generics), Exxua, Fetzima, Pexeva, vilazodone hydrochloride tablets (Viibryd or generics), or Trintellix at any time in the past and discontinued its use, approve the Product that they have used.

3. If the patient cannot swallow or has difficulty swallowing tablets or capsules, approve generic escitalopram oral solution or generic paroxetine HCl oral suspension.

4. If the patient has suicidal ideation, approve Desvenlafaxine extended-release tablets (brand product), desvenlafaxine succinate extended-release tablets (Pristiq or generics), Exxua, Fetzima, Pexeva, vilazodone hydrochloride tablets (Viibryd or generics), or Trintellix.

REFERENCES

1. Wellbutrin SR® sustained-release tablets [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; April 2024.
2. Wellbutrin XL® extended-release tablets [prescribing information]. Bridgewater, NJ: Bausch Health; March 2024.
3. Aplenzin® extended-release tablets [prescribing information]. Bridgewater, NJ: Bausch Health; March 2024.
4. Forfivo XL extended-release tablets [prescribing information]. Pine Brook, NJ: Almatica; May 2024.
5. Auvelity® extended-release tablets [prescribing information]. New York, NY: Axsome; May 2024.
6. Exxua extended-release tablets [prescribing information]. Houston, TX: Fabre Kramer; September 2023.
7. Bupropion hydrochloride extended-release tablets (SR) [prescribing information]. Hauppauge, NY: ScieGen; May 2021.
8. Prozac® capsules [prescribing information]. Indianapolis, IN: Lilly; August 2023.

9. Paxil® tablets and oral suspension [prescribing information]. Weston, FL: Apotex; November 2024.
10. Zoloft® tablets, oral concentrate [prescribing information]. Morgantown, WV: Viatris; August 2023.
11. Celexa® tablets and oral solution [prescribing information]. North Chicago, IL: AbbVie; October 2023.
12. Paxil CR® controlled-release tablets [prescribing information]. Weston, FL: Apotex; February 2024.
13. Lexapro® tablets/oral solution [prescribing information]. North Chicago, IL: AbbVie; October 2023.
14. Pexeva® paroxetine mesylate tablets [prescribing information]. Roswell, GA: Sebela; August 2023.
15. Fluvoxamine maleate tablets [prescribing information]. Baudette, MN: ANI: August 2023.
16. Fluvoxamine extended-release capsules [prescribing information]. Malvern, PA: Endo; October 2023.
17. Sarafem® capsules [prescribing information]. Indianapolis, IN: Lilly; August 2023.
18. Viibryd® tablets [prescribing information]. North Chicago, IL: AbbVie; October 2023.
19. Trintellix® tablets [prescribing information]. Lexington, MA and Deerfield, IL: Takeda and Lundbeck; August 2023.
20. Brisdelle® capsules [prescribing information]. Georgetown, Grand Cayman: Legacy Pharma; February 2025.
21. Sertraline capsules [prescribing information]. Morristown, NJ: Almatica; August 2023.
22. Citalopram capsules [prescribing information]. Morristown, NJ: Almatica; August 2023.
23. Escitalopram capsules [prescribing information]. Morristown, NJ: Almatica; August 2025.
24. Cymbalta® capsules [prescribing information]. Indianapolis, IN: Lilly; August 2023.
25. Effexor XR® extended-release capsules [prescribing information]. Morgantown, WV: Viatris; August 2023.
26. Venlafaxine hydrochloride tablets [prescribing information]. Parsippany, NJ: Teva; August 2023.
27. Pristiq® extended-release tablets [prescribing information]. Philadelphia, PA: Wyeth; August 2023.
28. Venlafaxine extended-release tablets [prescribing information]. Cranbury, NJ: Sun; September 2023.
29. Venlafaxine besylate extended-release tablets [prescribing information]. Morristown, NJ: Almatica; August 2023.
30. Fetzima® extended-release capsules [prescribing information]. North Chicago, IL: AbbVie; April 2024.
31. Desvenlafaxine extended-release tablets [prescribing information]. Cranbury, NJ: Sun; August 2023.
32. Drizalma Sprinkle™ delayed-release capsules [prescribing information]. Cranbury, NJ: Sun; August 2023.
33. Savella® tablets [prescribing information]. Madison, NJ: Allergan; May 2024.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	Effective 07/01/2024.	05/29/2024
Annual Revision	**Brisdelle:** Brand Brisdelle removed from Step 2 of the policy; obsolete for ≥ 3 years.	05/21/2025
Selected Revision	**Sertraline capsules:** The descriptor "(brand)" was deleted after sertraline capsules in the list of Step 2 Products because sertraline capsules are now available as brand and generic products.	08/27/2025
Selected Revision	**Escitalopram capsules:** Brand escitalopram capsules added to the policy as a Step 2 product.	10/15/2025
Selected Revision	**Exxua:** Added to Step 2 of the policy. Exxua was included in the standard and high impact exception criterion allowing a patient currently taking or who has taken the Product at any time in the past and discontinued its use to receive the Product that they have	11/12/2025

	used and to the exception criterion allowing a patient who has suicidal ideation to receive the Product requested.	