


PHARMACY POLICY – 5.01.520

Antidepressants: Pharmacy Medical Necessity Criteria for Brands

Effective Date:	Jul. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Jun. 10, 2025	5.01.521 Pharmacologic Treatment of Neuropathy, Fibromyalgia, and Seizure Disorders
Replaces:	N/A	5.01.605 Medical Necessity Criteria for Pharmacy Edits

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Introduction

Drugs are grouped into classes. Drugs can be in the same class because they work in the same way, have a similar chemical structure, or are used for the same purpose. There are a number of drug classes for antidepressant drugs. These include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). MAOIs and TCAs were the first drugs developed in the 1950s and are considered first-generation antidepressants. Because antidepressants like SSRIs and SNRIs were developed later they are considered second-generation antidepressants. Like most drugs, second-generation antidepressants come in both brand and generic form. The active ingredients in generic drugs are chemically identical to the active ingredients in brand name drugs. Because generic drugs have the same active ingredients as brand name drugs, they are usually tried first. This policy describes when brand-name second-generation antidepressants may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Condition & Drug	Medical Necessity
Anxiety <ul style="list-style-type: none"> Aplenzin ER (bupropion hydrobromide ER) Bupropion XL 450mg tablet Celexa (citalopram) Citalopram capsule Cymbalta (duloxetine) Desvenlafaxine ER Drizalma Sprinkle (duloxetine DR) Effexor XR (venlafaxine ER) Fetzima (levomilnacipran) Forfivo XL (bupropion ER) Lexapro (escitalopram) Paxil (paroxetine) Paxil CR (paroxetine ER) Pristiq (desvenlafaxine) Prozac (fluoxetine) Remeron (mirtazapine) Sertraline capsule Symbyax (olanzapine and fluoxetine) Trintellix (vortioxetine) Venlafaxine Besylate ER Viibryd (vilazodone) Wellbutrin SR (bupropion SR) Wellbutrin XL (bupropion ER) Zoloft (sertraline) 	<p>Brand selective serotonin reuptake inhibitor (SSRI), serotonin/norepinephrine reuptake inhibitor (SNRI), and any second-generation antidepressant, when used to treat anxiety, may be considered medically necessary when:</p> <ul style="list-style-type: none"> The individual has had a trial and failure of two generic SSRIs (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline) <p>OR</p> <ul style="list-style-type: none"> Has had a trial and failure of two generic SNRIs (e.g., desvenlafaxine, duloxetine, venlafaxine) <p>OR</p> <ul style="list-style-type: none"> Has had a trial and failure of one generic SSRI and one generic SNRI <p>Note: For diagnosis of diabetic peripheral neuropathy, chronic musculoskeletal pain or fibromyalgia, see Related Policies.</p>
Depression <ul style="list-style-type: none"> Aplenzin ER (bupropion hydrobromide ER) 	<p>Brand selective serotonin reuptake inhibitor (SSRI), serotonin/norepinephrine reuptake inhibitor (SNRI), and any second-generation antidepressant, when used to treat depression, may be considered medically necessary when:</p>

Condition & Drug	Medical Necessity
<ul style="list-style-type: none"> • Auvelity (dextromethorphan and bupropion) • Bupropion XL 450mg tablet • Celexa (citalopram) • Citalopram capsule • Cymbalta (duloxetine) • Desvenlafaxine ER • Drizalma Sprinkle (duloxetine DR) • Effexor XR (venlafaxine ER) • Exxua (gepirone) • Fetzima (levomilnacipran) • Forfivo XL (bupropion ER) • Lexapro (escitalopram) • Paxil (paroxetine) • Paxil CR (paroxetine ER) • Pristiq (desvenlafaxine) • Prozac (fluoxetine) • Raldesy (trazodone oral solution) • Remeron (mirtazapine) • Sertraline capsule • Symbyax (olanzapine and fluoxetine) • Trintellix (vortioxetine) • Venlafaxine Besylate ER • Viibryd (vilazodone) • Wellbutrin SR (bupropion SR) • Wellbutrin XL (bupropion ER) • Zoloft (sertraline) 	<ul style="list-style-type: none"> • The individual has had a trial and failure of two generic second-generation antidepressants (e.g., fluoxetine, sertraline, venlafaxine, bupropion, mirtazapine) <p>Auvelity (dextromethorphan and bupropion) when used to treat depression, may be considered medically necessary when:</p> <ul style="list-style-type: none"> • The individual has had a trial and failure of two generic second-generation antidepressants (e.g., fluoxetine, sertraline, venlafaxine, bupropion, mirtazapine) <p>Exxua (gepirone) when used to treat depression, may be considered medically necessary when:</p> <ul style="list-style-type: none"> • The individual has had a trial and failure of two generic second-generation antidepressants (e.g., fluoxetine, sertraline, venlafaxine, bupropion, mirtazapine) <p>Raldesy (trazodone oral solution) when used to treat depression, may be considered medically necessary when:</p> <ul style="list-style-type: none"> • The individual has had a trial and failure of generic trazodone tablet <p>OR</p> <ul style="list-style-type: none"> • Documentation is provided that the oral solution is clinically necessary (e.g., trouble swallowing, etc.) <p>AND</p> <ul style="list-style-type: none"> • The dose is limited to 400 mg per day <p>Note: For diagnosis of diabetic peripheral neuropathy, chronic musculoskeletal pain or fibromyalgia, see Related Policies.</p>

Drug	Not Medically Necessary
As listed	All other uses of the medications listed in this policy are considered not medically necessary.



Drug	Investigational
As listed	The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.

Length of Approval	
Approval	Criteria
Initial authorization	<p>Non-formulary exception reviews for all drugs listed in this policy may be approved up to 12 months.</p> <p>All other reviews for all drugs listed in this policy may be approved up to 3 years.</p>
Re-authorization criteria	<p>Non-formulary exception reviews for all drugs listed in this policy may be approved up to 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.</p> <p>All other reviews for all drugs listed in this policy may be approved up to 3 years as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.</p>

Documentation Requirements
<p>The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:</p> <ul style="list-style-type: none"> Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

Coding

N/A



Related Information

Benefit Application

This policy applies to all pharmacy benefit contracts that include pharmacy prior authorization edits.

This policy is managed through the pharmacy benefit.

Evidence Review

Description

Pathophysiology of Depression

While the pathology of depression is far from completely understood, it is apparent that both heredity and environmental factors play a part. Genetic microarray techniques are being used to identify candidate genes, with the hope of developing a pharmacogenomic approach to predicting which drugs will be most effective in each individual. However, this knowledge is still in its infancy, and its practical application will be some time in the future. For now, practitioners must continue using empiric approaches to treatment, both pharmacologic and otherwise.

Disease Burden

More than 18 million Americans suffer from depression. Over 15% will experience at least one major depressive episode during their lifetimes. Exact prevalence rates are difficult to determine because of the extent to which depression goes unreported. It occurs twice as frequently in women as in men. A meta-analysis showed that depressed persons have a 1.5-2 fold increased risk of mortality.

In 2000, the economic burden of depression in the US was estimated to be \$83.1 billion. Indirect costs include related mortality and morbidity, as well as significant amounts of absenteeism and



presenteeism that can impact workplace productivity. Quality of life of individuals and those around them also suffer.

Pharmacotherapy

An overview of the various treatment modalities used in depression was provided in Lancet by Ebmeier et al. Treatments include a variety of cognitive behavioral approaches, psychotherapy, treatment with antidepressant medications and in severely resistant cases, electroconvulsive therapy. Of the nonpharmacologic treatment modalities, cognitive behavioral approaches have the best supporting evidence. Drugs used to treat depression include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOI) and several agents with combinations of serotonergic, noradrenergic and dopaminergic activity.

This policy applies to the following medications:

- Single Source Brand (SSB) selective serotonin reuptake inhibitor (SSRI), serotonin/norepinephrine reuptake inhibitor (SNRI) and any other SSB second-generation antidepressants (antidepressants other than tricyclic and MAOI agents).

Summary of Evidence

Current evidence from head-to-head comparative trials of second-generation antidepressants, systematic reviews, and meta-analyses indicates these agents are of comparable efficacy and effectiveness as measured by HAM-D or MADRS response (>50% improvement), though one study reported a statistically superior but modest improvement in MADRS score with escitalopram compared to citalopram. Overall, the data support for a meaningful difference is not compelling.

Evidence from four small comparative effectiveness trials failed to provide compelling evidence of the superiority of escitalopram. In the one study that showed a statistically significant difference in the primary endpoint (change from baseline in MADRS score), the effect size was modest, and p value was barely significant.

Two longer-term (≥6 month) efficacy and safety studies of duloxetine (Cymbalta) duloxetine have been published, and the manufacturer supplied data on two unpublished trials. Although not compelling, evidence now supports the relative safety of longer-term (6 month to 1 year)



use of duloxetine for the treatment of major depressive disorder. Other evidence also shows comparable efficacy with venlafaxine and comparable onset of effect with escitalopram.

A meta-analysis of 117 small randomized controlled trials including 25,928 individuals compared 12 “new generation” antidepressants for efficacy and tolerability. The authors concluded that escitalopram and sertraline offered the best combination of efficacy and individual acceptability. Of the two, they felt that sertraline might be the best choice when starting treatment, because it has the best balance between efficacy, safety and cost. Although well-designed, this study is limited by the size and heterogeneity of the individual trials that were included. In particular, the evidence supporting superiority of escitalopram over citalopram is based on 5 small trials, all of which were manufacturer-sponsored. There is no clinical reason to expect a meaningful difference between these two agents, assuming that the doses of the S-isomer are equal.

A similar meta-analysis of 203 studies yielded no substantial differences among agents. The authors concluded that the body of existing evidence does not favor selection of one particular antidepressant over the others based on efficacy or effectiveness.

US guidelines for the treatment of adults with depression from the American Psychiatric Association recommend use of antidepressants as preferred initial treatment or as a part of a preferred initial treatment regimen for most individuals with any level of severity of MDD. Initial choice of medication should consider anticipated side effects, safety or tolerability of side effects for individual individuals, individual preference, quantity and quality of clinical trial data, and cost. Based on these factors, the APA indicates SSRIs, desipramine, nortriptyline, bupropion, venlafaxine, and mirtazapine are likely to be effective for most individuals.

2009 Update

A literature search was performed for March 2009 through December 2009. No published randomized studies were found that would change the policy statements.

2011 Update

Updated to incorporate reference to newly US Food and Drug Administration (FDA-approved indication for Cymbalta in chronic musculoskeletal pain). No other significant updates to the literature were found.

2012 Update

Updated to allow for recent availability of generic escitalopram; thus, trial of generic citalopram is no longer a specific requirement for access to Lexapro. No other significant updates to the literature were found.

2014 Update

Updated to include newly available generic duloxetine and Khedezla, a new venlafaxine extended release product. No other significant changes to the literature were found at this time.

2015 Update

Expanded the indication of Major Depressive Disorder to Depressive Disorders; Expanded the indication of Generalized Anxiety Disorder to Anxiety Disorders. Updated these new expanded indications with separate criteria: For individuals with Depressive Disorders, trial and failure of at least two generically available second generation antidepressants; or individuals with Anxiety Disorders, trial and failure of at least two generically available SSRIs, or at least one generically available SSRI and one generically available SNRI.

2016 Update

A literature search was performed for April 1, 2015 through December 6, 2016. No published randomized studies were found that would change existing policy statements.

2017 Update

A literature search was performed for July 1, 2016 through November 2, 2017. No published studies were found that would change existing policy statements.



2019 Update

A literature search was performed for December 1, 2018 through November 30, 2019. No published studies were found that would change existing policy statements.

2020 Update

No changes to policy statement. Combined depression and anxiety criteria into one table. Added a table documenting that all other uses of brand SSRI, SNRI, and any second- generation antidepressant for this policy are considered not medically necessary. Added a Length of Approval and Documentation Requirements table to policy.

2021 Update

A literature search was performed for July 1, 2020 through June 30, 2021. No published studies were found that would change existing policy statements.

2022 Update

Reviewed UpToDate on "Unipolar major depression in adults: Choosing initial treatment". Evidence presented continues to support initial treatment with an SSRI or SNRI rather than other antidepressants. No new information was identified that would require changes to this policy.

2023 Update

No new information was identified that would require changes to this policy.

2024 Update

Added Exxua (gepirone) coverage criteria for the treatment of depression.



2025 Update

Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

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History

Date	Comments
12/13/05	Add to Prescription Drug Section - New Policy—effective January 1, 2006.
08/08/06	Replace Policy - Policy reviewed with literature search by Pharmacy and Therapeutic Committee on July 25, 2006. Policy statement updated with exenatide and thiazolidinediones added as medically necessary; Policy Guidelines and Rationale sections updated; references added.
05/08/07	Replace Policy - Policy statement for exenatide updated with additional criteria; Policy Guidelines updated to reflect addition to policy statement. Reviewed by P&T on March 27, 2007.
06/12/07	Replace Policy - Policy statement on coverage criteria for exenatide (Byetta), sitagliptin and esomeprazole (Nexium®) expanded; medically necessary indications for 5HT3 antagonists, Actiq and Fentora added to policy statement. Policy Guidelines updated and Rationale updated; references added
12/11/07	Replace Policy - Policy reviewed with literature search by Pharmacy and Therapeutic Committee on May 15, 2007. Policy statement updated to include Pregabalin as either medically necessary or investigational under the criteria. Acyclovir, famciclovir and valacyclovir as medically necessary under criteria. References added.
04/08/08	Replace Policy - Policy updated with literature search by Pharmacy. Policy statement was updated to include fibromyalgia as a medically necessary indication under Pregabalin. References added.
12/16/08	Replace Policy - Policy updated with literature search by Pharmacy. Policy statement updated to include the use of leukotriene modifiers for the treatment of allergic rhinitis refractory to nasal corticosteroids under the medically necessary indication.
02/10/09	New PR Policy PR.5.01.520 - Policy information regarding antidepressants deleted from PR.5.01.605 and addressed in this new policy.
01/12/10	Replace Policy - Policy reviewed with literature search; no change to the policy statement. References added.
05/10/11	Replace Policy - Medically necessary policy statement on branded SSRI, SSNI and second generation antidepressants updated to require trial and failure two generic antidepressants as a condition to be met, where it was previously only one; chronic musculoskeletal pain has been added as an exception to the investigational indications for use of duloxetine (Cymbalta®). Title changed to "Antidepressants: Pharmacy Medical Necessity Criteria for Brands." Reviewed by P&T in March 2011.



Date	Comments
09/11/12	Replace policy. Policy updated with literature review. Policy Guidelines section updated to allow for recent availability of generic escitalopram; thus, trial of generic citalopram is no longer a specific requirement for access to Lexapro.
07/08/13	Replace policy. Policy Guidelines updated with Desvenlafaxine, a recently released second-generation SSRI used for treating depression, which may be approved following the failure of two generics, one being venlafaxine. Clarification was added to the policy that it is managed through the member's pharmacy benefit; this is now listed in the header and within the coding section.
12/04/13	Replace policy. Policy section updated with Khedezla™ added to the list of SSRIs which may be approved when criteria are met.
03/10/14	Replace policy. Cymbalta removed from the scope of policy; prior authorization is no longer required. (NOTE: This is a non-formulary medication; therefore, prior authorization would be required for closed formulary.)
10/13/14	Interim update. Clarification made that policy applies to branded SSRI (selective serotonin reuptake inhibitor) and second generation antidepressants (antidepressants other than tricyclic and MAOI agents) from a single source.
07/14/15	Annual Review. Policy updated with literature review. The following updates were performed: Expanded the indication of Major Depressive Disorder to Depressive Disorders; Expanded the indication of Generalized Anxiety Disorder to Anxiety Disorders; Updated these new expanded indications with separate criteria: For patients with Depressive Disorders, trial and failure of at least two generically available second generation antidepressants, and for patients with Anxiety Disorders, trial and failure of at least two generically available SSRIs, or at least one generically available SSRI and one generically available SNRI.
10/13/15	Interim Update. Requirements of venlafaxine trial for Pristiq, Khedezla or Desvenlafaxine were removed. All brand antidepressants will have same criteria of any 2 generics first. No change to policy statement.
01/01/17	Annual Review, approved December 13, 2016. No published randomized studies were found that would change existing policy statements. Minor correction was made to the 2015 update, i.e., addition of "trial and failure of a generically available SNRI."
12/01/17	Annual Review, approved November 21, 2017. No published randomized studies were found that would change existing policy statements.
11/01/18	Annual Review, approved October 26, 2018. No changes to policy.
01/01/20	Annual Review, approved December 10, 2019. No changes to policy statement.
12/01/20	Annual Review, approved November 3, 2020. No changes to policy statement. Combined depression and anxiety criteria into one table. Added a table documenting that all other uses of brand SSRI, SNRI, and any second- generation antidepressant for this policy are considered not medically necessary. Added a Length of Approval and Documentation Requirements table to policy.



Date	Comments
09/01/21	Annual Review, approved August 3, 2021. No changes to policy statement.
11/01/22	Annual Review, approved October 10, 2022. No changes to policy statement. Changed the wording from "patient" to "individual" throughout the policy for standardization.
06/01/23	Annual Review, approved May 22, 2023. No changes to policy statement.
04/01/24	Annual Review, approved March 11, 2024. Added Exxua (gepirone) coverage criteria for the treatment of depression.
01/01/25	Interim Review, approved December 10, 2024. Added Auvelity (dextromethorphan and bupropion) coverage criteria for the treatment of depression. Added to policy the drug names for brand antidepressants. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
03/01/25	Annual Review, approved February 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.
07/01/25	Interim Review, approved June 10, 2025. Added coverage for Raldesy (trazodone oral solution) for the treatment of depression.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premera All Rights Reserved.

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