Clinical Policy: Clomipramine (Anafranil)

Reference Number: CP.PMN.197
Effective Date: 06.01.19
Last Review Date: 05.25
Line of Business: Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Clomipramine (Anafranil™) is a tricyclic antidepressant.

FDA Approved Indication(s)

Anafranil is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD).

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Anafranil is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Obsessive-Compulsive Disorder (must meet all)**:**

1. Diagnosis of OCD;
2. Failure of 2 selective serotonin reuptake inhibitors (SSRIs), each used for at least 4 weeks at up to maximally indicated doses unless clinically significant adverse effects are experienced or all are contraindicated;
3. For Anafranil requests, member must use generic clomipramine, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 250 mg per day.

Approval duration: 12 months

B. Autistic Disorder (off-label) (must meet all)**:**

1. Diagnosis of autistic disorder;
2. Failure of a 4 week trial of fluoxetine at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
3. For Anafranil requests, member must use generic clomipramine, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 250 mg per day.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Anafranil for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For Anafranil requests, member must use generic clomipramine, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, new dose does not exceed 250 mg per day;

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
MAOI: monoamine oxidase inhibitor
OCD: obsessive-compulsive disorder
SSRI: selective serotonin reuptake inhibitor

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
citalopram (Celexa®)	OCD*: 40 mg PO/day	40 mg/day
escitalopram (Lexapro®)	Autistic disorder*: 20 mg PO/day	40 mg/day
fluoxetine (Prozac®)	OCD: 20-80 mg PO/day Autistic disorder*: 20-40 mg PO/day	80 mg/day
fluvoxamine (Luvox®)	OCD: 100-300 mg PO/day	300 mg/day
paroxetine (Paxil®, Pexeva®)	OCD: 40-60 mg PO/day	60 mg/day
sertraline (Zoloft®)	OCD: 50-200 mg PO/day	200 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

Appendix C: Contraindications

- Contraindication(s): coadministration with a monoamine oxidase inhibitor (MAO), including linezolid and intravenous methylene blue, or within 14 days of MAOI discontinuation due to increase risk of serotonin syndrome; hypersensitivity to clomipramine or other tricyclic antidepressants; during the acute recovery period after a myocardial infarction
- Boxed warning(s): Antidepressants increased the risk compared to placebo of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders.

Appendix D: General Information

- Per the American Psychiatric Association guidelines for OCD, first-line therapies are serotonin reuptake inhibitors, which include clomipramine and all SSRIs. SSRIs are generally preferred prior to clomipramine due to their better safety profile.
  - While some meta-analyses of placebo-controlled trials suggest greater efficacy for clomipramine than for fluoxetine, fluvoxamine, and sertraline, the results of head-to-head trials directly comparing clomipramine and SSRIs do not support this.
- Autism spectrum disorder:
  - Per the American Academy of Child and Adolescent Psychiatry guidelines, pharmacotherapy may be used when there is a specific target symptom or comorbid condition. Clomipramine and fluoxetine are both serotonin reuptake inhibitors which have been shown to decrease repetitive behaviors in randomized controlled trials.

- Citalopram is another serotonin reuptake inhibitor which was evaluated in a randomized controlled trial; however, there was no significant difference in repetitive behaviors compared to placebo.

- Per the American Academy of Pediatrics guidelines, atypical antipsychotics (aripiprazole, risperidone), anticonvulsants (valproic acid, divalproex sodium), and SSRIs (fluoxetine, fluvoxamine) are therapies that may be used for repetitive behaviors; clomipramine is not included.
  - Valproic acid, divalproex sodium, and fluvoxamine do not have compendial support (Clinical Pharmacology, Micromedex) for use in autism.
  - Aripiprazole and risperidone are FDA-approved and compendia-supported only for irritability associated with autistic disorder.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
OCD	Adults: Initially 25 mg PO QD; increase as tolerated to 100 mg during the first 2 weeks Pediatrics: Initially 25 mg PO QD; increase as tolerated to 3 mg/kg or 100 mg, whichever is smaller, during the first 2 weeks	Adults: 250 mg/day Pediatrics: 3 mg/kg/ day or 200 mg/day, whichever is smaller
Autistic disorder*	Adults: Initially 25 mg PO QD; increase if needed to 75-100 mg Pediatrics: Initially 25 mg PO QD; increase if needed to 3 mg/kg or 200 mg, whichever is smaller	Adults: 250 mg/day Pediatrics: 3 mg/kg/ day or 200 mg/day, whichever is smaller

**Off-label*

VI. Product Availability

Capsules: 25 mg, 50 mg, 75 mg

VII. References

1. Anafranil Prescribing Information. Webster Groves, MO: SpecGx LLC; March 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/019906s043lbl.pdf. Accessed January 16, 2025.
2. Koran LM, Hanna GL, Hollandar E, et al. Practice guideline for the treatment of patients with obsessive-compulsive disorder. Arlington, VA: American Psychiatric Association; July 2007. Available at: http://www.psychiatryonline.org/guidelines.
3. Dixon L, Perkins D, Calmes C. Guideline watch (March 2013): practice guideline for the treatment of patients with obsessive-compulsive disorder. Arlington, VA: American Psychiatric Association; March 2013. Available at: http://www.psychiatryonline.org/guidelines.
4. Volkmar F, Siegel M, Woodbury-Smith M, et al. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2014; 53(2): 237-257.
5. Hyman SL, Levy SE, Myers SM, et al. Identification, evaluation, and management of children with autism spectrum disorder. Pediatrics. 2020; 145 (1): e20193447.

6. Micromedex® DRUGDEX® [Internet database]. Ann Arbor, Michigan: Merative™. Updated periodically. Accessed February 27, 2025.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2021 annual review: no significant changes; removed references to CP.CPA.09 as the Commercial line of business is not included in this policy; updated Appendix D to include AAP ASD guideline recommendations; references reviewed and updated.	01.11.21	05.21
2Q 2022 annual review: no significant changes; references reviewed and updated.	02.06.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.05.22	
2Q 2023 annual review: no significant changes; added template requirement to use generic clomipramine; references reviewed and updated.	02.06.23	05.23
2Q 2024 annual review: no significant changes; references reviewed and updated.	01.16.24	05.24
Revised continued therapy criteria to allow continuity of care for all indications.	06.05.24	08.24
2Q 2025 annual review: no significant changes; references reviewed and updated.	02.27.25	05.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.
Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.