Clinical Policy: Clomipramine (Anafranil)
Reference Number: HIM.PA.149
Effective Date: 03.13.18
Last Review Date: 05.18
Line of Business: HIM

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 contraindicated or clinically significant adverse effects are experienced;
      3. Dose does not exceed 250 mg/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. Dose does not exceed 250 mg/day.
      Approval duration: 12 months
   
   C. Premature Ejaculation (off-label) (must meet all):
      1. Diagnosis of premature ejaculation;
      2. Failure of 2 of the following SSRIs: fluoxetine, paroxetine, or sertraline, each used at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
      3. Dose does not exceed 25 mg prior to intercourse (no more than 4 capsules/month).
      Approval duration: 12 months
D. Other diagnoses/indications
1. Refer to HIM.PHAR.21 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy
A. All Indications in Section I (must meet all):
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed (a or b):
   a. OCD or autistic disorder: 250 mg/day;
   b. Premature ejaculation: 25 mg prior to intercourse (no more than 4 capsules/month).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to HIM.PHAR.21 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – HIM.PHAR.21 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>citalopram (Celexa®)</td>
<td>OCD*: 40 mg PO/day</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>escitalopram (Lexapro®)</td>
<td>OCD*: 20 mg PO/day</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>fluoxetine (Prozac®)</td>
<td>OCD: 20-60 mg PO/day Autistic disorder*: 20-40 mg PO/day Premature ejaculation*: 5-20 mg PO/day</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>fluvoxamine (Luvox®)</td>
<td>OCD: 100-200 mg PO/day</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/ Maximum Dose</td>
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<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td>paroxetine (Paxil®, Pexeva®)</td>
<td>OCD: 40-60 mg PO/day Premature ejaculation*: 10-40 mg PO/day or 20 mg PO 3-4 hours before intercourse</td>
<td>60 mg/day</td>
</tr>
<tr>
<td></td>
<td>Premature ejaculation*: 25-200 mg PO/day or 50 mg PO 4-8 hours before intercourse</td>
<td>200 mg/day</td>
</tr>
</tbody>
</table>

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: General Information

- **Contraindications:**
  - Concurrent use with a monoamine oxidase inhibitor or within 14 days of stopping a monoamine oxidase inhibitor due to the increased risk of serotonin syndrome
  - Concurrent use with linezolid or intravenous methylene blue due to the increased risk of serotonin syndrome
  - Use during the acute recovery period after a myocardial infarction due to cardiovascular effects (e.g., decrease in blood pressure, tachycardia, electrocardiogram changes)

- 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.

- Per the American Academy of Child and Adolescent Psychiatry guidelines for autism spectrum disorder, 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 Urological Association guidelines for premature ejaculation, the following serotonin reuptake inhibitors have demonstrated benefit over placebo in clinical trials: fluoxetine, paroxetine, sertraline, and clomipramine.
  - Studies suggest that nefazodone, citalopram, and fluvoxamine, on the other hand, are ineffective for premature ejaculation.
  - Both continuous (daily) and situational (prior to intercourse) dosing regimens are used to manage premature ejaculation. One has not been shown to be more effective than the other.
V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
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<tbody>
<tr>
<td>OCD</td>
<td>Adults: Initially 25 mg PO QD; increase as tolerated to 100 mg during the first 2 weeks</td>
<td>Adults: 250 mg/day</td>
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<tr>
<td></td>
<td>Pediatrics: Initially 25 mg PO QD; increase as tolerated to 3 mg/kg or 100 mg, whichever is smaller, during the first 2 weeks</td>
<td>Pediatrics: 3 mg/kg/day or 200 mg/day, whichever is smaller</td>
</tr>
<tr>
<td>Autistic disorder*</td>
<td>Adults: Initially 25 mg PO QD; increase if needed to 75-100 mg</td>
<td>Adults: 250 mg/day</td>
</tr>
<tr>
<td></td>
<td>Pediatrics: Initially 25 mg PO QD; increase if needed to 3 mg/kg or 200 mg, whichever is smaller</td>
<td>Pediatrics: 3 mg/kg/day or 200 mg/day, whichever is smaller</td>
</tr>
<tr>
<td>Premature ejaculation*</td>
<td>25-50 mg PO QD or 25 mg PO 4-24 hours prior to intercourse**</td>
<td>See regimen</td>
</tr>
</tbody>
</table>

*Off-label
**Note: Only the situational (prior to intercourse) dosing regimen is covered

VI. Product Availability
Capsules: 25 mg, 50 mg, 75 mg

VII. References

Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>Policy created</td>
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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.

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