Pseudobulbar Affect (PBA)

FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosage &amp; Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuedexta® (dextromethorphan hydrobromide and quinidine sulfate) capsule</td>
<td>Treatment of pseudobulbar affect (PBA)</td>
<td>Initial: 1 capsule orally daily for initial 7 days</td>
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<td>Maintenance: after 7 days; 1 capsule orally every 12 hours</td>
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</table>

CLINICAL RATIONALE

Pseudobulbar affect (PBA) is characterized as having abrupt episodes of uncontrollable laughter or crying that are incongruent or independent of mood.2,3 The episodes are involuntary and are disconnected from external circumstances and internal mood states. PBA has also been referred to as emotional lability, reflex crying, and involuntary emotion expression disorder.2,3 PBA occurs secondary to underlying neurological disorder, such as amyotrophic lateral sclerosis (ALS), extrapyramidal and cerebellar disorders (Parkinson’s disease, multiple system atrophy, progressive supranuclear palsy), multiple sclerosis (MS), Alzheimer's disease, or damage to central nervous system, such as stroke, traumatic brain injury, dementia, and brain tumors.3

PBA is often confused with other psychiatric disorders, such as depression, and could be overlooked or under reported when treating other neurological disorders, such as ALS and MS. A studied noted that when compared to patients without PBA, patients with PBA had a higher prevalence of anxiety symptoms and poorer social functioning. PBA has been associated with a higher prevalence of diagnosable psychiatric disorders, and about 30%–35% of patients with PBA are depressed.3

The goal of treatment of PBA is to diminish the severity and frequency of episodes. Tricyclic antidepressants (TCA) and selective serotonin reductase inhibitors (SSRIs) are most commonly used to treat PBA.3,4 Dopaminergic medications, such as levodopa and amantadine, have been used but with lower response rates. The serotonergic action of SSRIs and TCAs appears to be the most significant therapeutic mechanism in treatment of PBA, via an increase in availability of serotonin at the synapses in corticolimbic and cerebellar pathways. The efficacy of antidepressants appears to be unrelated to the treatment of depression, based upon several pieces of evidence: 1) the onset of action may occur within a few days, which is faster than expected for depression; 2) doses are lower than those usually used to treat depression; and 3) most patients with PBA are not depressed.3
Several studies compared antidepressants, fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), nortriptyline (Aventyl, Pamelor), or amitriptyline (Elavil), against placebo. Five studies were in stroke patients, one study in 12 MS patients found the medication reduced the number of laughing and weeping episodes more than placebo. Antidepressants also improved patient scores on screening tests used to assess emotions. Side effects varied depending on the medication used but were relatively mild.5

Nuedexta, combination dextromethorphan and quinidine, received FDA approval for treatment of PBA. Low-dose quinidine competitively inhibits cytochrome P450 2D6 to reduce hepatic metabolism of dextromethorphan, allowing for higher bioavailability.1,2,3

The efficacy of Nuedexta was demonstrated in one trial in patients with pseudobulbar affect (PBA). These patients had underlying amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS). The primary outcome measure of laughing and crying episodes, was statistically significantly lower in each dextromethorphan/quinidine arm compared to placebo, based on an analysis of the sums of the episode counts over the double-blind phase. The secondary endpoint was the Center for Neurologic Studies Lability Scale (CNS-LS), a seven-item self-report questionnaire with 3 items assessing crying and 4 assessing laughter. CNS-LS was analyzed based on the difference between the mean scores on day 84 and baseline, and was also statistically significantly lower in each dextromethorphan/quinidine arm compared to placebo.1

Safety1
A year-long study of Nuedexta in 533 neurological patients with PBA found significant improvements in PBA symptoms regardless of the underlying condition, with no signs of heart rhythm disorders or other serious side effects. However, only about half of the patients completed the trial. The study reported that nearly one-third of the participants quit because of side effects, including nausea, headache, dizziness, falls, and diarrhea. Although relatively mild, about 90 percent of participants experienced some side effects. There was, however, no evidence of any significant effect on heart rhythm.5

For additional clinical information see the Prime Therapeutics Formulary Chapters 11.3: Neuromuscular Agents.

REFERENCES
Pseudobulbar Affect (PBA) Prior Authorization with Quantity Limit

OBJECTIVE
The intent of the Pseudobulbar Affect (PBA) Prior Authorization (PA) program is to promote appropriate selection of patients for treatment according to FDA approved labeling and/or clinical guidelines. Approval will be granted for patients with a diagnosis of pseudobulbar affect. The criteria does not allow concomitant use of with a monoamine oxidase inhibitor (MAOI) or use of a MAOI within 14 days. The criteria also will not allow coverage in patients who have FDA labeled contraindications to the requested agent. Requests will be reviewed when patient-specific documentation has been provided.

TARGET AGENT
Nuedexta® (dextromethorphan hydrobromide and quinidine sulfate)

PROGRAM QUANTITY LIMIT

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuedexta (dextromethorphan hydrobromide and quinidine sulfate)</td>
<td>62609902300120 M, N, O, or Y</td>
<td>2 capsules</td>
<td></td>
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PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation
Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) will be approved when ALL of the following are met:

1. The patient has a diagnosis of pseudobulbar affect (PBA) AND
2. The patient has a diagnosis of amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS) AND
3. The prescriber is a specialist (i.e. neurologist, neuropsychologist, psychiatrist) or the prescriber has consulted with a specialist AND
4. The prescriber has provided a baseline number of laughing and/or crying episodes experienced by the patient AND
5. ONE of the following:
   a. The patient has tried and had an inadequate response to tricyclic antidepressant (TCA) (e.g., amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline) OR selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) in the past 180 days OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to TCA or SSRIs AND
6. The patient is NOT currently receiving a monoamine oxidase inhibitor (MAOI) (e.g., Marplan/isocarboxazid, Nardil/phenelzine, and Parnate/tranylcypromine) OR the patient’s MAOI will be discontinued at least 14 days prior to starting therapy with the requested agent AND
7. The patient does NOT have any FDA labeled contraindications to the requested agent AND
8. ONE of the following:
   a. The requested quantity (dose) does not exceed the program quantity limit
b. ALL of the following:
   i. The requested quantity (dose) is greater than the program quantity limit
      AND
   ii. The requested quantity (dose) does not exceed the maximum FDA labeled
dose
      AND
   iii. The requested quantity (dose) cannot be achieved with a lower quantity of
        a high strength that does not exceed the program quantity limit
        OR

c. ALL of the following:
   i. The requested quantity (dose) is greater than the program quantity limit
      AND
   ii. The requested quantity (dose) is greater than the maximum FDA labeled
dose
      AND
   iii. The prescriber has submitted documentation in support of therapy with a
        higher dose for the requested indication

Length of Approval: 6 months

Renewal Evaluation
Nuedexta (dextromethorphan hydrobromide and quinidine sulfate) will be approved when
ALL of the following are met:
   1. The patient has been previously approved for the requested agent through the Prime
      Therapeutics PA process
      AND
   2. The patient has a diagnosis of pseudobulbar affect (PBA)
      AND
   3. The patient has a diagnosis of amyotrophic lateral sclerosis (ALS) or multiple sclerosis
      (MS)
      AND
   4. The prescriber is a specialist (i.e. neurologist, neuropsychologist, psychiatrist) or the
      prescriber has consulted with a specialist
      AND
   5. The patient has experienced a decrease in laughing and/or crying episodes from
      baseline
      AND
   6. The patient is NOT currently receiving a monoamine oxidase inhibitor (MAOI) (e.g.,
      Marplan/isocarboxazid, Nardil/phenelzine, and Parnate/tranylcypromine) OR the
      patient’s MAOI will be discontinued at least 14 days prior to starting therapy with the
      requested agent
      AND
   7. The patient does NOT have any FDA labeled contraindications to the requested agent
      AND
   8. ONE of the following:
      a. The requested quantity (dose) does not exceed the program quantity limit
         OR
      b. ALL of the following:
         i. The requested quantity (dose) is greater than the program quantity limit
            AND
         ii. The requested quantity (dose) does not exceed the maximum FDA labeled
             dose
             AND
iii. The requested quantity (dose) cannot be achieved with a lower quantity of a high strength that does not exceed the program quantity limit

**OR**

c. ALL of the following:
   i. The requested quantity (dose) is greater than the program quantity limit
   **AND**
   ii. The requested quantity (dose) is greater than the maximum FDA labeled dose
   **AND**
   iii. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication

**Length of Approval:** 12 months
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE

The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL

The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR

2. The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

   OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria