Pseudobulbar Affect (PBA) Prior Authorization with Quantity Limit Program Summary

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

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

FDA APPROVED INDICATIONS AND DOSAGE[1]

Agent(s)	Indication(s)	Dosage
Nuedexta® (dextromethorphan hydrobromide and quinidine sulfate) capsule	Treatment of pseudobulbar affect (PBA)	Initial: 1 capsule orally once daily for 7 days Maintenance: 1 capsule orally every 12 hours

CLINICAL RATIONALE

Pseudobulbar affect (PBA) is characterized as abrupt episodes of uncontrollable laughter and/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 occurs when neural pathways that modulate emotional responses in the brain are interrupted, particularly descending pathways from the frontal lobes to the cerebellum.[6] Medical conditions which result in a disruption of those pathways, such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), multiple sclerosis (MS), Alzheimer's disease (AD), or traumatic brain injury (TBI), can produce the hallmark symptoms of PBA.[2,3,4,6]

PBA is under-reported due to often being mistaken for a sign of depression or simply a general reaction to the burden of the underlying neurological disease. Rather, PBA is a specific condition itself, distinct from other types of emotional lability that may occur in patients with neurological disease or injury.[2,6] The presence of PBA can usually be detected by simply asking the patient or caregiver if they have a tendency to laugh or cry for no reason or have an exaggerated response to emotional situations.[2] A self-administered questionnaire that screens for laughing and crying symptoms, called the Center for Neurologic Study – Lability Scale (CNS-LS), has been validated in ALS and MS. Scores range from one to five for each question, resulting in a total score of seven (no excess emotional lability) to 35 (severe excess emotional lability). A cutoff of 13 accurately predicted neurologists' clinical diagnosis in 82% of ALS patients. Such a cutoff for patients with MS was less accurate, predicting the neurologist's diagnosis 78% of the time in cases with low specificity, leading to a high number of false positives. Raising the cutoff to 17 for patients with MS improved the specificity without meaningfully affecting the sensitivity.[3]

The goal of treatment of PBA is to diminish the severity and frequency of episodes. In patients with TBI or stroke, the need for treatment may diminish as recovery occurs and neurological function is restored. In MS, ALS, PD, and AD, however, treatment is likely to be needed long-term.[2] The primary neurotransmitter abnormalities involved in PBA are serotonin and glutamate, and pharmacologic treatments have focused on drugs that modulate these neurotransmitters.[2,3,5,6] Tricyclic antidepressants (TCAs) and selective serotonin reuptake

inhibitors (SSRIs) are most commonly used to treat PBA.[2,3,4,6] Dopaminergic medications, such as carbidopa/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. As a qualitative indicator that PBA is distinct from depression, patient responses to antidepressants typically occur at lower doses than used for depression, and time to observable alleviation of PBA symptoms may be shorter compared to alleviation of depression symptoms.[3,6]

Nuedexta, currently the only FDA-approved drug for the treatment of PBA, is a combination of dextromethorphan and quinidine. Dextromethorphan has CNS activity both as an uncompetitive antagonist of the NMDA-sensitive glutamate receptor and as a sigma-1 receptor agonist. In addition, it shows affinity for monoamine transporters resulting in a modulatory effect on neurotransmission involving glutamate, serotonin, and noradrenalin.[2,6] Dextromethorphan is the pharmacologically-active component of Nuedexta but is rapidly catabolized in the liver by cytochrome P450 2D6 (CYP2D6). Low-dose quinidine competitively inhibits CYP2D6, but at such a low dose level that it is generally well tolerated and does not affect the safety profile of the combination treatment.[1-3,6] Though PBA is still believed highly under-reported and under-treated, the availability of an FDA labeled therapy for the treatment of PBA has motivated increased vigilance for the condition and encourages clinicians to look for the condition among their new and established patients.[2,6]

Efficacy
The efficacy of Nuedexta was demonstrated in one trial of 326 patients with PBA and underlying ALS or MS. The primary outcome measure of laughing and crying episodes was based on an analysis of the sums of the episode counts over the double-blind phase. The daily PBA episode rate was 46.9% lower in the 30 mg/10 mg dextromethorphan/quinidine arm, and 49% lower in the 20 mg/10 mg dextromethorphan/quinidine arm, compared to placebo. The secondary endpoint was the CNS-LS scores, 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. There were no clinically important differences between Nuedexta (20 mg/10 mg) and the 30 mg/10 mg arm.[1,2,6]

Safety
Nuedexta has the following contraindications:[1]

- Concomitant use with quinidine, quinine, or mefloquine.
- Patients with a history of quinidine, quinine or mefloquine-induced thrombocytopenia, hepatitis, or other hypersensitivity reactions.
- Patients with known hypersensitivity to dextromethorphan.
- Use with an MAOI or within 14 days of stopping an MAOI. Allow 14 days after stopping Nuedexta before starting an MAOI.
- Prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, or heart failure.
- Complete atrioventricular (AV) block without implanted pacemaker, or patients at high risk of complete AV block.
- Concomitant use with drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine or pimozide).

REFERENCES

1. Nuedexta Prescribing Information. Avanir Pharmaceuticals, Inc. June 2019.
2. Cummings J, Gilbart J, Andersen G. Pseudobulbar Affect – A Disabling but Under-Recognised Consequence of Neurological Disease and Brain Injury. *Eur Neurol Rev.* 2013;8(2):74–81.
3. Ahmed A, Simmons Z. Pseudobulbar Affect: Prevalence and Management. *Ther Clin Risk Manag.* 2013;9:483–489.

4. Galvex-Jimenez N, et al. Symptom-Based Management of Amyotrophic Lateral Sclerosis. UpToDate. Last updated March 2020. Literature review current through August 2020.
5. Gordon D. Pseudobulbar Affect: Research points to an effective treatment for different neurological conditions. *Neurology Now*. 2015 Jan;10(6):56-58.
6. Chen JJ. Pharmacotherapeutic Management of Pseudobulbar Affect. *Am J Manag Care.* 2017;23:S345-S350.

Pseudobulbar Affect (PBA) Prior Authorization with Quantity Limit

TARGET AGENT
Nuedexta® (dextromethorphan hydrobromide and quinidine sulfate)

Brand (generic)	GPI	Multisource Code	Quantity Limit
Nuedexta (dextromethorphan hydrobromide and quinidine sulfate)			
20 mg/10 mg capsule	62609902300120	M, N, O, or Y	2 capsules

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent 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 has provided a baseline number of laughing and/or crying episodes experienced by the patient
   AND
4. ONE of the following:
   A. The patient has tried and had an inadequate response to a tricyclic antidepressant (TCA) (e.g., amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline) OR a selective serotonin reuptake inhibitor (SSRI) (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) used for the requested indication
   OR
   B. The patient has an intolerance or hypersensitivity to TCA or SSRI therapy
   OR
   C. The patient has an FDA labeled contraindication to ALL TCAs AND SSRIs
   OR
   D. The patient is currently being treated with the requested agent as indicated by ALL of the following:
      i. A statement by the prescriber that the patient is currently taking the requested agent
      AND
      ii. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      AND
      iii. The prescriber states that a change in therapy is expected to be ineffective or cause harm
   OR
   E. The prescriber has provided documentation that ALL TCAs AND SSRIs 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
   AND
5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, neuropsychologist, psychiatrist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
   AND

6. The patient will NOT be using the requested agent in combination with OR within 14 days of a monoamine oxidase inhibitor (MAOI) [e.g., Marplan (isocarboxazid), Nardil (phenelzine), Parnate (tranylcypromine)]
   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 for the requested indication
         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher 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 for the requested indication
         AND
      iii. The prescriber has provided information in support of therapy with a higher dose for the requested indication

Length of Approval: 6 months

Renewal Evaluation
Target Agent will be approved when ALL of the following are met:
1. The patient has been previously approved for the requested agent through the plan's Prior Authorization 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 patient has experienced a decrease in laughing and/or crying episodes from baseline
   AND
5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, neuropsychologist, psychiatrist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
   AND
6. The patient will NOT be using the requested agent in combination with OR within 14 days of a monoamine oxidase inhibitor (MAOI) [e.g., Marplan (isocarboxazid), Nardil (phenelzine), Parnate (tranylcypromine)]
   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 for the requested indication
        AND
        iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher 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 for the requested indication
        AND
        iii. The prescriber has provided information in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months