Nocturia Prior Authorization with Quantity Limit Program Summary

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

This is a FlexRx Standard and GenRx Standard program.

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

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

FDA APPROVED INDICATIONS AND DOSAGE\(^1,6\)

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Indication(s)</th>
<th>Dosage and Administration</th>
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</thead>
</table>
| **Noctiva™** (desmopressin acetate) nasal spray | Treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void | \(< 65\) years of age who are not at increased risk for hyponatremia: use one spray of 1.66 mcg in either nostril nightly approximately 30 minutes before going to bed  
\(\geq 65\) years of age or younger patients at risk for hyponatremia: use 0.83 mcg nightly, which can be increased to one spray of 1.66 mcg after at least 7 days, if needed, provided the serum sodium has remained normal |
| **Nocturna®** (desmopressin acetate) Tablets | Treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void | Women: 27.7 mcg one hour before bedtime  
Men: 55.3 mcg one hour before bedtime |

CLINICAL RATIONALE

The International Continence Society (ICS) defines nocturia as the complaint that the individual wakes at night one or more times to void. Nocturnal polyuria occurs when an increased proportion of the 24-hour urine output occurs at night.\(^2\) Evidence suggests nocturia becomes bothersome to patients at two or more voids per night.\(^3\) The prevalence of nocturia is equal in both genders, however age distribution differs between genders. One-third of young women (18-29 years old) in a study reported nocturia at least once per night, compared to 1 in 9 of young men. Moreover, the prevalence of nocturia increases with age twice as rapidly in men compared to women. By the sixth decade of life, the percentage of nocturia reported in both genders is the same.\(^3\) Population studies have confirmed that nocturia increases with age and is common in the elderly. It was found that the majority of elderly men and women experience clinically significant nocturia: 29% to 59.3% in men and 28.3 to 61.5% in women aged \(\geq 70\) years experienced 2 or more voids per night.\(^3\)
Management of nocturia may require multifaceted approach. Treatment of underlying medical conditions should be optimized and may reduce nocturia symptoms. Nocturia has been associated with many comorbidities including hypertension, diabetes, obstructive sleep apnea, and major depressive disorder. First line management of nocturia involves behavior modifications such as reduction in alcoholic or caffeinated beverages, afternoon naps, compression stockings, and restriction of evening fluid intake. Several pharmacologic options are used for nocturia. 5-alpha reductase inhibitors (i.e., dutasteride, finasteride) are commonly used in men for treatment of prostatic obstruction and lower urinary tract symptoms. Alpha-blockers (i.e., alfuzosin, doxazosin, tamsulosin, terazosin) have shown modest effects on nocturia. Anticholinergic agents (i.e., oxybutynin, tolterodine) are useful in treatment of overactive bladder and also used in the treatment of nocturia. Loop diuretics (i.e., furosemide, bumetanide) are also used to regulate urine production in the daytime in order to decrease urine production during sleep.

Desmopressin use aims to increase vasopressin in patients with nocturia, which results in reduced urine production by the kidneys. One hundred and twenty-seven people, with ≥2 voids nightly, were randomized to receive either an escalating dose of desmopressin or placebo. After 3 weeks, a clinically significant reduction (> 50% reduction in mean number of voids) was found in 33% of the treatment arm, compared to 11% of the placebo arm (P = 0.0014). A study examined the efficacy of desmopressin, which was maintained for the duration of long-term treatment. Patients taking varying doses (25 µg, 50 µg, and 100 µg) of desmopressin sublingual “melt” tablets for 52 weeks had a mean decrease in the number of nocturnal voids of 1.4, 1.8, and 2.1 voids, respectively. For Nocdurna, two studies were completed, one for women and one for men. In Study 1, 237 women with nocturia were randomized to receive Nocdurna 27.7mcg (n=121) or placebo (n=116) every night one hour before bedtime for 3 months. In Study 2, 230 men with nocturia were randomized to receive Nocdurna 55.3 mcg (n=102) or placebo (n=128) every night one hour before bedtime for 3 months. In both studies, endpoints were 1) the change in number of nocturia episodes per night from baseline and 2) a ‘33% responder status”, which was defined as a subject with a decrease of at least 33% in the mean number of nocturnal voids compared to baseline. In Study 1, Nocdurna patients had a -1.5 change from a baseline of 2.9 versus -1.2 for placebo. This equated to a -0.3 difference from placebo with a 95% CI of -0.5, -0.1. Probability of 33% responder status was 0.78 for Nocdurna, compared to 0.62 with placebo, leading to a 2.15 odds ratio with a 95% CI of 1.36, 3.41. In Study 2, Nocdurna patients had a -1.3 reduction from a baseline of 3.0. Placebo patients had a reduction of -0.9, leading to a -0.4 difference from placebo (95% CI= -0.6 to -0.2). Probably of 33% responder status was 0.67 on Nocdurna versus 0.50 on placebo, leading to an odds ratio of 2.02 (95% CI=1.30, 3.14).

Desmopressin therapy is not recommended for use in patients with baseline hyponatremia or impaired renal function (eGFR < 60ml/min).

Safety
Noctiva is contraindicated in patients with the following conditions due to an increased risk of severe hyponatremia:
- Hyponatremia or a history of hyponatremia
- Polydipsia
- Primary nocturnal enuresis
- Concomitant use with loop diuretics
- Concomitant use with systemic or inhaled glucocorticoids
- Renal impairment with an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m²
- Known or suspected syndrome of inappropriate antidiuretic hormone (SIADH) secretion
- During illnesses that can cause fluid or electrolyte imbalance, such as gastroenteritis, salt-wasting nephropathies, or systemic infection
Noctiva is contraindicated in patients with the following conditions because of fluid retention increases the risk of worsening the underlying condition:
  • Congestive heart failure (New York Heart Association Class II to IV)
  • Uncontrolled hypertension

Nocdurna is contraindicated in patients with the following conditions due to an increased risk of severe hyponatremia:
  • Hyponatremia or a history of hyponatremia
  • Polydipsia
  • Concomitant use with loop diuretics or systemic or inhaled glucocorticoids
  • Renal impairment with an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m²
  • Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
  • During illnesses that can cause fluid or electrolyte imbalance

Nocdurna is contraindicated in patients with the following conditions because of fluid retention increases the risk of worsening the underlying condition:
  • Congestive heart failure
  • Uncontrolled hypertension

In response to an FDA alert and request December 2007, DDAVP (desmopressin nasal spray 0.01% solution) is no longer indicated for primary nocturnal enuresis due to risk for development of severe hyponatremia that can result in seizures and death. A black box warning is listed in the prescribing information for DDAVP, Noctiva, and Nocdurna products for risk of hyponatremia.¹,⁵

For additional clinical information see the Prime Therapeutics Formulary Chapters 8.

REFERENCES
Nocturia Prior Authorization with Quantity Limit

TARGET AGENT
Noctiva (desmopressin acetate)
Nocdurna (desmopressin acetate)

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>Noctiva (desmopressin acetate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.83 mcg nasal spray</td>
<td>30201010101620</td>
<td>M, N, O, Y</td>
<td>1 bottle (3.8 grams)/30 days</td>
</tr>
<tr>
<td>1.66 mcg nasal spray</td>
<td>30201010101630</td>
<td>M, N, O, Y</td>
<td>1 bottle (3.8 grams)/30 days</td>
</tr>
<tr>
<td>Nocdurna (desmopressin acetate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.7 mcg tablet</td>
<td>30201010100710</td>
<td>M, N, O, Y</td>
<td>27.7 mcg/day</td>
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<tr>
<td>55.3 mcg tablet</td>
<td>30201010100715</td>
<td>M, N, O, Y</td>
<td>55.3 mcg/day</td>
</tr>
</tbody>
</table>

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

Target Agent will be approved when ALL of the following are met:

1. If the target agent is Noctiva, the patient is 50 years of age or over
2. The patient has a diagnosis of nocturnal polyuria confirmed by a 24-hour urine collection
3. The requested agent will be used to treat nocturia due to nocturnal polyuria
4. The prescriber has confirmed that the patient’s serum sodium concentration is within normal range [between 135 to 145 mEq/L (mmol/L) or within testing laboratory’s normal range]
5. The patient has tried and had an inadequate response to behavior modifications for nocturia (e.g. physician monitored restriction of fluids, afternoon naps, elevation of legs, compression stockings)
6. ONE of the following:
   a. The patient has tried and had an inadequate response to generic oral desmopressin
   OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to oral desmopressin
7. The patient will NOT be using a loop diuretic concomitantly with the requested agent
8. The patient will NOT be using systemic or inhaled glucocorticoids with the requested agent
9. The patient is NOT pregnant
10. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
11. ONE of the following:
   a. The requested quantity (dose) is NOT greater than 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) is less than or equal to the maximum FDA labeled dose
      AND
   iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the 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

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 Prime Therapeutics PA process
   AND
2. The patient has had clinical benefit with the requested agent
   AND
3. The prescriber has confirmed that the patient’s serum sodium concentration is within normal range [between 135 to 145 mEq/L (mmol/L) or within testing laboratory’s normal range]
   AND
4. The patient will NOT be using a loop diuretic concomitantly with the requested agent
   AND
5. The patient will NOT be using systemic or inhaled glucocorticoids with the requested agent
   AND
6. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
   AND
7. ONE of the following:
   a. The requested quantity (dose) is NOT greater than 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) is less than or equal to the maximum FDA labeled dose
         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the 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