Clinical Policy: Desmopressin Acetate (DDAVP, Stimate, Nocdurna, Noctiva)

Reference Number: ERX.NPA.48
Effective Date: 09.01.17
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Revision Log

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

Description
Desmopressin acetate (DDAVP®, Stimate®, Nocdurna®, Noctiva™) is a synthetic vasopressin analog.

FDA Approved Indication(s)
DDAVP and Stimate are indicated for the treatment of patients with:
- Mild to moderate classic von Willebrand's disease (VWD; type I) with factor VIII levels greater than 5%
- Hemophilia A with factor VIII coagulant activity levels greater than 5%

DDAVP is also indicated for the management of central (cranial) diabetes insipidus and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region.

Noctiva and Nocdurna are indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

Limitation(s) of use:
- DDAVP and Stimate are not indicated for the treatment of hemophilia A with factor VIII coagulant activity levels equal to or less than 5%, or for the treatment of hemophilia B, or in patients who have factor VIII antibodies.
- DDAVP and Stimate are not indicated for the treatment of severe classic VWD (type I) and when there is evidence of an abnormal molecular form of factor VIII antigen.
- DDAVP is ineffective for the treatment of nephrogenic diabetes insipidus.
- Noctiva has not been studied in patients less than 50 years of age.

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that DDAVP injection, Stimate, Nocdurna, and Noctiva are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Polyuria and Central Diabetes Insipidus (must meet all)**:**

1. Diagnosis of one of the following (a or b):
   a. Central (cranial) diabetes insipidus;
   b. Temporary polyuria and polydipsia following head trauma or surgery in the pituitary region;
2. Prescribed by or in consultation with an endocrinologist;
3. Age ≥ 12 years;
4. Request is for DDAVP injection;
5. Failure of desmopressin tablets, unless contraindicated, clinically significant adverse effects are experienced, or documentation supports inability to swallow tablets;

6. Dose does not exceed 4 mcg per day.

Approval duration: 6 months

B. Congenital Hemophilia A (must meet all)**:**
1. Diagnosis of congenital hemophilia A (factor VIII deficiency);
2. Prescribed by or in consultation with a hematologist;
3. Age ≥ 3 months;
4. Request is for DDAVP injection or Stimate for one of the following uses (a, b, or c):
   a. Control and prevention of bleeding episodes;
   b. Perioperative management;
   c. Routine prophylaxis to prevent or reduce the frequency of bleeding episodes;
5. Factor VIII coagulant activity levels are > 5%;
6. Member does not have factor VIII antibodies;
7. Dose does not exceed any of the following (a or b):
   a. DDAVP injection: 0.3 mcg/kg per dose;
   b. Stimate: 300 mcg per day.

Approval duration: 6 months

C. Von Willebrand Disease (must meet all)**:**
1. Diagnosis of VWD type 1 or type 2;
2. Prescribed by or in consultation with a hematologist;
3. Age ≥ 3 months;
4. Request is for DDAVP injection or Stimate for one of the following uses (a, b, or c):
   a. Control and prevention of bleeding episodes;
   b. Perioperative management;
   c. Routine prophylaxis to prevent or reduce the frequency of bleeding episodes;
5. Factor VIII coagulant activity levels are > 5%;
6. Dose does not exceed any of the following (a or b):
   a. DDAVP injection: 0.3 mcg/kg per dose;
   b. Stimate: 300 mcg per day.

Approval duration: 6 months

D. Nocturia (must meet all)**:**
1. Diagnosis of nocturia due to nocturnal polyuria;
2. Age ≥ 18 years;
3. Request is for Nocdurna or Noctiva;
4. Dose does not exceed any of the following (a or b):
   a. Nocdurna: 1 tablet per day (27.7 mcg for women, 55.3 mcg for men);
   b. Noctiva: 1.66 mcg per day (1 bottle per 30 days).

Approval duration: 12 months

E. Other diagnoses/indications
1. Refer to ERX.PA.01 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 a health plan affiliated with Envolve Pharmacy Solutions 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 any of the following (a, b, c, or d):
   a. DDAVP injection: 4 mcg per day for polyuria or diabetes insipidus and 0.3 mcg/kg per dose for hemophilia A or VWD;
   b. Stimate: 300 mcg per day;

c. Nocdurna: 1 tablet per day (27.7 mcg for women, 55.3 mcg for men);
d. Noctiva: 1.66 mcg per day (1 bottle per 30 days).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 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 – ERX.PA.01 or evidence of coverage documents;

B. Noctiva for primary nocturnal enuresis.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

DDAVP: 1-deamino-8-D-arginine vasopressin
eGFR: estimated glomerular filtration rate
FDA: Food and Drug Administration
SIADH: syndrome of inappropriate antidiuretic hormone
VWD: von Willebrand disease

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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
desmopressin acetate oral tablets (DDAVP®)	**Polyuria and Central Diabetes Insipidus** 0.05 mg PO BID, titrated to a maintenance dose in the range of 0.1-1.2 mg divided into 2-3 daily doses as needed to obtain adequate antidiuresis	1.2 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.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - DDAVP injection: moderate to severe renal impairment (creatinine clearance < 50 mL/min), hyponatremia or a history of hyponatremia
  - Stimate: none reported
  - Noctiva: primary nocturnal enuresis; hyponatremia or a history of hyponatremia; polydipsia; concomitant use with loop diuretics or systemic/inhaled glucocorticoids; renal impairment with an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2; 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; congestive heart failure (New York Heart Association class II to IV); uncontrolled hypertension
  - Nocdurna: hyponatremia or a history of hyponatremia; polydipsia; concomitant use with loop diuretics or systemic/inhaled glucocorticoids; renal impairment with an eGFR below 50 mL/min/1.73 m^2; SIADH secretion;, during illnesses that can cause fluid or electrolyte imbalance;, heart failure; uncontrolled hypertension
- Boxed warning(s):
  - DDAVP injection, Stimate: none reported
  - Noctiva: hyponatremia

Appendix D: General Information

- The American Urology Association defines nocturnal polyuria as the production of greater than 20 to 33% of total 24-hour urine output during the period of sleep, which is age-dependent with 20% for younger individuals and 33% for elderly individuals.
- Nocturnal polyuria was defined in the Noctiva clinical trials as nighttime urine production exceeding one-third of the 24-hour urine production.
- Noctiva is contraindicated in the treatment of primary nocturnal enuresis because of reports of hyponatremic-related seizures in pediatric patients treated with other intranasal forms of desmopressin. Desmopressin acetate tablets, however, are FDA-approved for this use.

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Desmopressin injection (DDAVP)	Central diabetes insipidus	2 to 4 mcg IV or SC daily, usually in 2 divided doses	4 mcg/day
	Hemophilia A, VWD	0.3 mcg/kg IV or SC as needed	0.3 mcg/kg/dose
Desmopressin nasal spray (Stimate)	Hemophilia A, VWD	One spray per nostril	300 mcg/dose
Desmopressin sublingual tablet (Nocdurna)	Nocturnal polyuria	Women: 27.7 mcg PO QD one hour before bedtime Men: 55.3 mcg PO QD one hour before bedtime	Women: 27.7 mcg/day; Men: 55.3 mcg/day
Desmopressin nasal spray (Noctiva)	Nocturnal polyuria	One spray in either nostril approximately 30 minutes before bedtime; dose varies by age and hyponatremia risk: Patients < 65 years without increased risk for hyponatremia: 1.66 mcg/spray Patients ≥ 65 years or younger patients at risk for hyponatremia: 0.83 mcg/spray (may titrate to 1.66 mcg after at least 7 days with normal sodium levels)	1.66 mcg/day

VI. Product Availability

Drug Name	Availability
Desmopressin injection (DDAVP)	Ampule: 4 mcg/mL (1 mL) Vial: 4 mcg/mL (10 mL)
Desmopressin nasal spray (Stimate)	Bottle with spray pump: 25 sprays of 150 mcg (2.5 mL)
Desmopressin sublingual tablet (Nocdurna)	Sublingual tablets: 27.7 mcg, 55.3 mcg
Desmopressin nasal spray (Noctiva)	Nasal spray: 3.5 mL bottle (30 effective 0.1 mL doses of either 0.83 mcg or 1.66 mcg)

VII. References

1. DDAVP Injection Prescribing Information. Parsippany, NJ: Ferring Pharmaceuticals; July 2021. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=651f6fee-a2c7-431b-8d5d-58b156c72244. Accessed November 27, 2021.
2. Desmopressin tablets Prescribing Information. Parsippany, NJ: Actavis Pharmaceuticals, Inc.; September 2014. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=43bd65ca-0b1c-42c9-bbcd-7a97d3287581. Accessed November 27, 2021.

3. Nocdurna Prescribing Information. Parsippany, NJ: Ferring Pharmaceuticals; November 2020. Available at: www.nocdurna.com. Accessed November 27, 2021.
4. Noctiva Prescribing Information. Chesterfield, MO: Avadel Specialty Pharmaceuticals, LLC; December 2017. Available at: www.noctiva.com. Accessed November 4, 2020.
5. Stimate Prescribing Information. King of Prussia, PA: CSL Behring LLC; June 2013. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=30d4c387-b99c-49f8-a8bd-de23fdafb739http://labeling.cslbehring.com/PI/US/Stimate/EN/Stimate-Prescribing-Information.pdf. Accessed November 27, 2021.
6. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia.* Jan 2013; 19(1): e1-47.
7. Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF): Database of treatment guidelines. Available at https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed October 29, 2019.
8. Van Kerrebroeck P, Abrams P, Chaikin D et al. The standardisation of terminology in nocturia: Report from the standardization sub-committee of the International Continence Society. Neurourol Urodyn 2002; 21: 179.
9. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders (Revised August 2020). MASC Document #263. Available at: https://www.hemophilia.org/sites/default/files/document/files/263_treatment.pdf. Accessed November 4, 2020.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2018 annual review: no significant changes; references reviewed and updated.	06.27.18	08.18
Added criteria for DDAVP injection and Stimate; references reviewed and updated.	07.09.18	11.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	09.26.18	02.19
RT4: added Nocdurna to the policy.	06.21.19	
1Q 2020 annual review: no significant changes; references reviewed and updated.	10.29.19	02.20
1Q 2021 annual review: no significant changes; references reviewed and updated.	11.04.20	02.21
1Q 2022 annual review: no significant changes; references reviewed and updated.	11.27.21	02.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

be bound by the foregoing terms and conditions, in addition to the Site Use Agreement for Health Plans associated with Envolve Pharmacy Solutions.