# NDA/BLA Multi-Disciplinary Review and Evaluation

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| **Application Type** | NDA |
| **Application Number(s)** | 219873 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | April 25, 2025 |
| **Received Date(s)** | April 25, 2025 |
| **PDUFA Goal Date** | February 25, 2026 |
| **Division/Office** | Division of General Endocrinology (DGE)/Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN) |
| **Review Completion Date** | February 24, 2026 |
| **Established/Proper Name** | desmopressin acetate |
| **(Proposed) Trade Name** | Desmopressin Acetate Oral Solution |
| **Pharmacologic Class** | Antidiuretic hormone |
| **Code name** | Arginine vasopressin |
| **Applicant** | Eton Pharmaceuticals, Inc. |
| **Dosage form** | Oral solution: 0.05 mg/mL |
| **Applicant proposed Dosing Regimen** | • Recommended starting dose is 0.05 mg twice daily and should be individually adjusted to the optimum therapeutic dose.<br>• The dosage of Desmopressin Acetate Oral Solution must be determined for each individual patient and adjusted according to the diurnal pattern response estimated by adequate duration of sleep and adequate water turnover. |
| **Applicant Proposed Indication(s)/Population(s)** | As antidiuretic replacement therapy for patients 2 years of age and older in the management of central diabetes insipidus (b) (4) [redacted] |
| **Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication** | Neurohypophyseal diabetes insipidus/Arginine Vasopressin Deficiency (AVP-D) |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | For the the management of central diabetes insipidus as antidiuretic replacement therapy for addults and pediatric patients |
| **Recommended SNOMED CT Indication Disease Term for each Indication** (if applicable) | Neurohypophyseal diabetes insipidus//Arginine Vasopressin Deficiency (AVP-D) |

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|---|---|
| **Recommended Dosing Regimen** | • Recommended starting dose is 0.05 mg twice daily and should be individually adjusted to the optimum therapeutic dose.<br>• The dosage of Desmopressin Acetate Oral Solution must be determined for each individual patient and adjusted according to the diurnal pattern response estimated by adequate duration of sleep and adequate water turnover. |

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## Reviewers of Multi-Disciplinary Review and Evaluation

| | |
|---|---|
| **Regulatory Project Manager** | Elizabeth Solomon |
| **Nonclinical Reviewer** | Dongyu Guo |
| **Nonclinical Supervisor** | David Carlson |
| **Office of Clinical Pharmacology Reviewer(s)** | Li Wang |
| **Office of Clinical Pharmacology Team Leader(s)** | Li Li |
| **Clinical Reviewer** | Geanina Roman-Popovenuic |
| **Clinical Team Leader** | Shannon Sullivan / Theresa Kehoe |
| **Statistical Reviewer** | NA |
| **Statistical Team Leader** | NA |
| **Cross-Disciplinary Team Leader** | Shannon Sullivan / Theresa Kehoe |
| **Associate Director for Labeling** | LaiMing Lee |
| **Division Director (DGE) designated signatory** | Theresa Kehoe |

## Additional Reviewers of Application

| | |
|---|---|
| **OPQ** | Mitchell McCloskey, Zhengfu Wang, Lotika Bajaj, Joyce Crich, Chaoying Ma, Alexander Gontcharov, Grafton Adams |
| **Microbiology** | Aditi Das, Elizabeth Bearr |
| **OPDP** | Koung Lee, Susannah O'Donnell, Lonics Carter, Marcia Williams |
| **OSIS** | Xikui Chen, Mei Ou |
| **OSE/DMEPA** | Peggy Rahbani, Yevgeniya Kogan |
| **Other** | |

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSIS=Office of Study Inteegrity and Surveillance
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

**Signatures**

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
| Nonclinical Reviewer | Dongyu Guo, PhD | OCHEN/DPT-CHEN | Sections: 5 | **Select one:** _X_ Authored ___ Approved |
| | **Signature:** DONGYU GUO -S Digitally signed by DONGYU GUO -S Date: 2026.02.23 14:39:33 -05'00' | | | |
| Nonclinical Supervisor | David Carlson, PhD | OCHEN/DPT-CHEN | Sections: 5 | **Select one:** ___ Authored _X_ Approved |
| | **Signature:** DAVID B. CARLSON -S Digitally signed by DAVID B. CARLSON -S Date: 2026.02.23 14:44:44 -05'00' | | | |
| Clinical Pharmacology Reviewer | Li Wang, PhD | OCP/DCEP | Sections: 6 and 19.4 | **Select one:** _X_ Authored ___ Approved |
| | **Signature:** LI WANG -S Digitally signed by LI WANG -S Date: 2026.02.23 14:56:40 -05'00' | | | |
| Clinical Pharmacology Team Leader | Li Li, PhD | OCP/DCEP | Section: 6 and 19.4 | **Select one:** ___ Authored _X_ Approved |
| | **Signature:** Li Li -S Digitally signed by Li Li -S Date: 2026.02.23 15:02:15 -05'00' | | | |
| Clinical Reviewer | Geanina Roman-Popoveniuc, MD | OCHEN/DGE | Section:1, 2, 3, 4, 7, 8.2, 8.4, 16.2 | **Select one:** _X_ Authored ___ Approved |
| | **Signature:** GEANINA ROMAN-POPOVENIUC -S Digitally signed by GEANINA ROMAN-POPOVENIUC -S Date: 2026.02.23 16:46:26 -05'00' | | | |
| Clinical Team Leader | Theresa Kehoe, MD | OCHEN/DGE | Section: All | **Select one:** ___ Authored _X_ Approved |
| | **Signature:** (See appended electronic signature page) | | | |

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
| Associate Director for Labeling | LaiMing Lee, PhD | OCHEN/DGE | Section: 11 | **Select one:**<br>_X_ Authored<br>___ Approved |
| | **Signature:** Lai M. Lee -S Digitally signed by Lai M. Lee -S Date: 2026.02.23 16:49:00 -05'00' | | | |
| Division Director (Clinical) | Theresa Kehoe, MD | OCHEN/DGE | Section: All | **Select one:**<br>___ Authored<br>_X_ Approved |
| | **Signature:** (See appended electronic signature page) | | | |

# Glossary

| | |
|---|---|
| AC | advisory committee |
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DHOT | Division of Hematology Oncology Toxicology |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ETASU | elements to assure safe use |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Conference on Harmonisation |
| IND | Investigational New Drug |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |
| OCS | Office of Computational Science |

| | |
|---|---|
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | prescribing information |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert (also known as Patient Information) |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1 Executive Summary

## 1.1. Product Introduction

Desmopressin Acetate Oral Solution 0.05 mg/mL is an antidiuretic hormone, indicated as replacement therapy in patients with central diabetes insipidus.

On April 25, 2025, Eton Pharmaceuticals, Inc (Applicant) submitted this New Drug Application (NDA) for Desmopressin Acetate Oral Solution 0.05 mg/mL under section 505(b)(2) of the of the Federal Food, Drug, and Cosmetic (FD&C) Act for the treatment of central diabetes insipidus, relying upon the Agency's findings of safety and effectiveness of the listed drug (LD) DDAVP (desmopressin acetate) oral tablets (NDA 019955, approved September 6, 1995).

The Applicant's submission includes:

1. A bioequivalence trial (24-VIN-0036) to establish the bioequivalence of Desmopressin Acetate Oral Solution against DDAVP tablets after a single oral dose administration under fasting and fed conditions.
2. A physicochemical assessment evaluating the Desmopressin Acetate Oral Solution drug substance and drug product.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted one bioequivalence (BE) trial, 24-VIN-0036, to establish bioequivalence between Desmopressin Acetate Oral Solution 0.05 mg/mL and DDAVP 0.2 mg tablet following administration of a single dose of 0.6 mg under fasting and fed conditions. The pharmacokinetic data from this trial demonstrated bioequivalence between the two drug products under fasting conditions only. Thus, the Division recommends approval of Desmopressin Acetate Oral Solution 0.05 mg/ml to be administered under fasting conditions.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Desmopressin Acetate Oral Solution is an antidiuretic hormone (ADH), indicated as replacement therapy in patients with central diabetes insipidus.

Central diabetes insipidus is a rare condition characterized by decreased production of ADH by pituitary gland and it presents with clinical symptoms of polyuria, polydipsia, nocturia, sleep disturbance, fatigue, dizziness and weight loss, which can be debilitating, if left untreated.

Synthetic desmopressin is considered the standard of care for treatment of central diabetes insipidus, and multiple demospressin products have been approved for this use, to include injectable, intranasal and oral tablet formulations. The goal of the treatment is to achieve symptomatic control. The desmopressin dose is titrated based on the clinical antidiuretic response, as measured by the urine volume and osmolality. There are currently no approved oral solution formulations of desmopressin for the treatment of central diabetes insipidus.

The Applicant is seeking approval of a new desmopressin oral solution via the 505(b)(2) regulatory pathway, and submitted one bioequivalence (BE) trial conducted to establish bioequivalence between Desmoressin acetate Oral Solution and DDAVP. Trial 24-VIN-0036 established bioequivalence between Desmopressin Acetate Oral Solution 0.05 mg/mL and DDAVP 0.2 mg tablet following administration of a single dose of 0.6 mg under fasting conditions. No new safety findings were observed during this trial, and the safety profile of Desmoressin Acetate Oral Solution remains favorable from a clinical perspective.

Therefore, DGE recommends approval of NDA 219873.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Central diabetes insipidus is a rare condition characterized by decreased production of antidiuretic hormone (ADH).<br>• The clinical signs and symptoms of central diabetes insipidus include polyuria and polydipsia. Other manifestations include nocturia, disturbed sleep, fatigue, postural dizziness and weight loss. | Central diabetes insipidus is a rare condition characterized by a constitution of symptoms, which, if untreated, can be debilitating. |
| Current Treatment Options | • Synthetic desmopressin is considered the standard of care for treatment of central diabetes insipidus.<br>• There are multiple desmopressin formulations available on the market, to include injectable, intranasal and oral tablet formulations.<br>• The dose of the drug should be titrated based on the clinical antidiuretic response, as measured by the urine volume and osmolality.<br>• There are currently no approved oral solution formulations of desmopressin for the treatment of central diabetes insipidus. | Desmopressin acetate is the standard of care for the treatment of central diabetes insipidus. Currently, there are no approved oral solution formulations of desmopressin. |
| Benefit | • Benefits of treatment with desmopressin therapy in patients with central diabetes insipidus include improvement in the clinical signs and symptoms, such as polyuria, polydipsia, nocturia, fatigue, and sleep disturbance. | Treatment with desmopressin in patients with central diabetes insipidus results in improvement in various symptoms of condition.<br>Availability of an oral solution formulation of desmoppresin will address the need for flexible and precise dose titration needed in certain patient populations, such as infants and young children. |
| Risk and Risk Management | • Overall, desmopressin therapy is well tolerated.<br>• Adverse events typically occur due to excessive fluid intake when urine output is limited, resulting in hyponatremia. Signs and symptoms of hyponatremia include headache, nausea/vomiting, decreased serum sodium, weight gain, restlessness, fatigue, lethargy, disorientation, | Desmopressin therapy is generally well-tolerated. AEs are typically related to hyponatremia resulting from excessive fluid intake and reduced urinary output. These AEs are adequately conveyed in the product label. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | depressed reflexes, loss of appetite, irritability, muscle weakness, muscle spasms and abnormal mental status. Severe symptoms due to severe hyponatremia may include seizure, coma and/or respiratory arrest. In order to decrease the risk of water intoxication with hyponatremia, fluid restriction is recommended. | |

## 1.4. Patient Experience Data

**Table 1 Patient Experience Data Relevant to this Application**

| | | | | |
|---|---|---|---|---|
| ☐ | **The patient experience data that were submitted as part of the application include:** | | | Section of review where discussed, if applicable |
| | ☐ | Clinical outcome assessment (COA) data, such as | | |
| | | ☐ | Patient reported outcome (PRO) | |
| | | ☐ | Observer reported outcome (ObsRO) | |
| | | ☐ | Clinician reported outcome (ClinRO) | |
| | | ☐ | Performance outcome (PerfO) | |
| | ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Natural history studies | | |
| | ☐ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | ☐ | Other: (Please specify): | | |
| ☐ | **Patient experience data that were not submitted in the application, but were considered in this review:** | | | |
| | ☐ | Input informed from participation in meetings with patient stakeholders | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Other: (Please specify): | | |
| X | **Patient experience data was not submitted as part of this application.** | | | |

# 2 Therapeutic Context

## 2.1. Analysis of Condition

Central diabetes insipidus, or arginine vasopressin deficiency (AVP-D)[1], is a condition characterized by decreased release of arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), resulting in water balance disruption and symptoms of polyuria, polydipsia, and electrolytes abnormalities such as hypernatremia.

Central diabetes insipidus (DI) is a rare disorder, with a reported prevalence of 1 in 25,000 individuals. [2] The prevalence of central DI is similar in females and males. The condition can have genetic, or acquired causes. Most cases are acquired, with less than 5% being attributable to genetic causes. Acquired central DI, especially in children and young adults, is caused by destruction or degeneration of the neurons that originate in the supraoptic and paraventricular nuclei of the hypothalamus. The known causes of these lesions include germinoma, craniopharyngioma, Langerhans cell histiocytosis, sarcoidosis, local inflammatory, autoimmune or vascular diseases and trauma from surgery or accident. However, between 20 and 50 % of cases are considered idiopathic.

The most common presenting symptom of central DI is significant polyuria, defined as urine output of >40-50 mL/kg/day (at least 2.5-3 L/day, but may exceed 8-16 L) and polydipsia, defined as a waterintake of >100 mL/kg/day. Individuals with polyuria and polydipsia complain of nocturia, disturbed sleep, fatigue, postural dizziness and weight loss. In children, symptoms range from frequent urination, nocturia, enuresis, constant thirst, irritability, sleep disturbance, failure to thrive and growth retardation.[3]

Treatment of choice for central DI consists of synthetic ADH, also known as desmopressin. Desmopressin is a synthetic analog of the endogenous hormone ADH, but with a 2000- to 3000-fold lower antidiuretic effect. Desmopressin can be administered orally, intranasally or parenterally.[3, 4] There is broad individual variation in the dosage required to control diuresis. Daily doses of oral preparations vary from 100 to 1200 mcg in three divided doses, for the intranasal preparation approximately 2-40 mcg given once or twice a day, and for the parenteral 0.1-1 mcg.

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[1] Arima H, et al. Working Group for Renaming Diabetes Insipidus. Changing the Name of Diabetes Insipidus: A Position Statement of the Working Group for Renaming Diabetes Insipidus. J Clin Endocrinol Metab. 2022; 108 (1): 1-3.
[2] Angelousi A, et al. New developments and concepts in the diagnosis and management of diabetes insipidus (AVP-deficiency and resistance). J Neuroendocrinol. 2023; 35(1): e13233.
[3] Di Iorgi N, et al. Diabetes insipidus--diagnosis and management. Horm Res Paediatr. 2012;77(2): 69-84.
[4] Patti G, et al. Central diabetes insipidus in children: Diagnosis and management. Best Pract Res Clin Endocrinol Metab. 2020; 34(5):101440.

It is crucial to monitor hyponatremia during treatment with desmopressin, as water retention can lead to sodium concentration changes that may cause brain injury. Symptoms of hyponatremia include headache, nausea, vomiting, lethargy, confusion, and seizures. Untreated, these symptoms can lead to coma and death.[3]

Other treatment options for central DI include a low-solute diet (low salt, low protein), thiazide diuretics, chlorpropamide, carbamazepine, and non-steroidal anti-inflammatory drugs.

## 2.2. Analysis of Current Treatment Options

FDA-approved therapies for the treatment of central diabetes insipidus include multiple formulations of desmopressin, to include injectable, intranasal and oral tablets. Refer to Table 2 for a list of approved desmopressin acetate products for the treatment of central diabetes insipidus. There are no desmopressin oral solution formulations approved for administration.

**Table 2. FDA-approved Therapies for Central Diabetes Insipidus**

| Product (s) Name (Application number/Company) | Dosage form/ Route of administration/ Strength | Year of Approval | Dosage recommendations |
|---|---|---|---|
| DDAVP (desmopressin acetate) (NDA 017922 – Ferring Pharms Inc.) | Solution/nasal/ 0.01% and<br><br>Spray, metered/nasal/ 0.01 mg/spray | 1978 | The recommended dosage in adults is 10 mcg once daily into one nostril up to 40 mcg once daily (or 40 mcg divided into two or three daily doses).<br><br>For pediatric patients 4 years of age and older, the recommended starting dosage of DDAVP Nasal Spray is 10 mcg once daily into one nostril. The dose can be titrated up to 30 mcg once daily (or 30 mcg divided into two daily doses, typically with 20 mcg given in the morning and 10 mcg given at nighttime).<br><br>If administered more than once a day, adjust for an adequate diurnal rhythm of urine output. |
| DDAVP (desmopressin acetate) (NDA 018938 – Nordic Pharma) | Injectable/injection/ 0.004 mg/mL | 1984 | The daily dose is 2 mcg to 4 mcg administered as one or two divided doses by subcutaneous or intravenous injection.<br><br>The dosage must be determined each patient and adjusted according to the pattern of response. |
| Concentraid (NDA 019776 - Ferring) | Solution/nasal/ 0.01% | 1990 | The usual dosage range in adults is 0.1 mL to 0.4 mL daily, either as a single dose or divided into two or three doses. Most adults require 0.2 mL daily in two divided doses.<br><br>For children aged 3 months to 12 years, the usual dosage range is 0.05 mL to 0.3 mL daily, either as |

| | | | |
|---|---|---|---|
| | | | a single dose or divided into two doses.<br><br>About 1/4 to 1/3 of patients can be controlled by a single daily dose of desmopressin acetate administered intranasally. Fluid restriction should be observed. The morning and evening doses should be separately adjusted for an adequate diurnal rhythm of water turnover. |
| DDAVP (desmopressin acetate) (NDA 019955 – Ferring Pharms Inc.) | Tablet/oral/<br>0.1 mg<br>0.2 mg | 1995 | It is recommended that patients be started on doses of 0.05 mg (1/2 of the 0.1 mg tablet) two times a day and individually adjusted to their optimum therapeutic dose. Total daily dosage should be increased or decreased in the range of 0.1 mg to 1.2 mg divided into two or three daily doses as needed to obtain adequate antidiuresis.<br><br>In younger pediatric patients, […] dosing should start at 0.05 mg (1/2 of the 0.1 mg tablet). |
| Desmopressin acetate (ANDA 074888 - Meitheal) | Injectable/injection/<br>0.004 mg/mL | 1997 | Same as DDAVP (desmopressin acetate) (NDA 018938 – Nordic Pharma) |
| Desmopressin acetate (ANDA 074830 - Bausch) | Spray, metered/nasal/<br>0.01 mg/spray | 1999 | Same as Concentraid (NDA 019776 - Ferring) |
| Minirin (NDA 021333 - Ferring) | Spray, metered/nasal/<br>0.01 mg/spray | 2002 | The recommended dosage in adults is 10 mcg once daily into one nostril up to 40 mcg once daily (or 40 mcg divided into two or three daily doses).<br><br>For pediatric patients 4 years of age and older, the recommended starting dosage of DDAVP Nasal |

| | | | |
|---|---|---|---|
| | | | Spray is 10 mcg once daily into one nostril. The dose can be titrated up to 30 mcg once daily (or 30 mcg divided into two daily doses, typically with 20 mcg given in the morning and 10 mcg given at nighttime).<br><br>If administered more than once a day, adjust for an adequate diurnal rhythm of urine output. |
| Desmopressin acetate (ANDA 076703 - Apotex) | Spray, metered/nasal/ 0.01 mg/spray | 2005 | Same as Concentraid (NDA 019776 - Ferring) |
| Desmopressin acetate (ANDA 077414 - Apotex) | Tablet/oral/ 0.1 mg 0.2 mg | 2006 | Same as DDAVP (desmopressin acetate) (NDA 019955 – Ferring Pharms Inc.) |
| Desmopressin acetate (NDA 021795 - Ferring) | Tablet/oral/ 0.1 mg 0.2 mg | 2008 | Individualize the dosage for each patient and adjust the dosage according to the diurnal pattern of response.<br><br>Recommended starting dose is 0.05 mg desmopressin acetate (half of the 0.1 mg Desmopressin Acetate Tablet) orally two times a day.<br><br>Titrate the daily dosage as needed. The usual dosage range is 0.1 mg daily to 1.2 mg daily orally divided into two or three daily doses.<br><br>Monitor response by measuring urine volume and osmolality. Monitoring measurements of plasma osmolality may also be useful. |
| Desmopressin acetate (ANDA 204695 – Sagent Pharms Inc) | Injectable/injection/ 0.004 mg/mL | 2017 | Same as DDAVP (desmopressin acetate) (NDA 018938 – Nordic Pharma) |

| | | | |
|---|---|---|---|
| Desmopressin acetate (ANDA 204751 – Sagent Pharms Inc) | Injectable/injection/ 0.004 mg/mL | 2017 | Same as DDAVP (desmopressin acetate) (NDA 018938 – Nordic Pharma) |
| Desmopressin acetate (ANDA 207880 – Heritage Pharma) | Tablet/oral/ 0.1 mg 0.2 mg | 2017 | Same as DDAVP (desmopressin acetate) (NDA 019955 – Ferring Pharms Inc.) |
| Desmopressin acetate (ANDA 091345 – Zydus Pharms) | Spray, metered/nasal/ 0.01 mg/spray | 2017 | Same as Concentraid (NDA 019776 - Ferring) |
| Desmopressin acetate (ANDA 208357 – Novast Labs) | Tablet/oral/ 0.1 mg 0.2 mg | 2019 | Same as DDAVP (desmopressin acetate) (NDA 019955 – Ferring Pharms Inc.) |
| Desmopressin acetate (ANDA 210371 – Abhai LLC) | Tablet/oral/ 0.1 mg 0.2 mg | 2019 | Same as DDAVP (desmopressin acetate) (NDA 019955 – Ferring Pharms Inc.) |
| Desmopressin acetate (ANDA 210218 – UBI) | Injectable/injection/ 0.004 mg/mL | 2020 | Same as DDAVP (desmopressin acetate) (NDA 018938 – Nordic Pharma) |
| Desmopressin acetate (ANDA 210223 – UBI) | Injectable/injection/ 0.004 mg/mL | 2020 | Same as DDAVP (desmopressin acetate) (NDA 018938 – Nordic Pharma) |
| Desmopressin acetate (ANDA 215961 – Dr Reddys) | Injectable/injection/ 0.004 mg/mL | 2022 | Same as DDAVP (desmopressin acetate) (NDA 018938 – Nordic Pharma) |
| Desmopressin acetate (ANDA 216922 – Gland) | Injectable/injection/ 0.004 mg/mL | 2022 | Same as DDAVP (desmopressin acetate) (NDA 018938 – Nordic Pharma) |
| Desmopressin acetate (ANDA 216904 – Gland) | Injectable/injection/ 0.004 mg/mL | 2023 | Same as DDAVP (desmopressin acetate) (NDA 018938 – Nordic Pharma) |
| Desmopressin acetate (ANDA 213095 – Aurobindo Pharma) | Tablet/oral/ 0.1 mg 0.2 mg | 2024 | Same as DDAVP (desmopressin acetate) (NDA 019955 – Ferring Pharms Inc.) |

*NDA = New Drug Application*
*ANDA = Abbreviated New Drug Application*
*Source: Approved labels at: drugs@FDA and https://dailymed.nlm.nih.gov*

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Desmopressin Acetate Oral Solution 0.05 mg/mL manufactured by Eton Pharmaceuticals is not currently marketed in US.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

On August 9, 2022, the Agency provided written responses during a Type B meeting with the Applicant under IND 172488 regarding the clinical data package to support a NDA submission for Desmopressin Acetate Oral Solution, in which the Agency noted that the proposal to rely on the evidence of safety and efficacy demonstrated for a reference listed drug was acceptable provided that an adequate scientific bridge between Desmopressin Acetate Oral Solution and the reference listed drug could be established.

On July 11, 2024, the Applicant (Eton Pharmaceuticals) submitted the opening-IND phase 1 trial titled "An Open Label, Balanced, Randomized, Single-Dose, Three-Treatment, Three- Sequence, Three-Period, Three-way Crossover Oral Bioequivalence Study of Desmopressin Acetate Oral Solution, 0.05 mg/mL (at Dose of 0.6 mg/12 mL) of Eton Pharmaceuticals, Inc., USA comparing with that of DDAVP® Tablets (desmopressin acetate) 0.2 mg [at dose of 0.6 mg (0.2 mg X 3 Tablets)] of Ferring Pharmaceuticals Inc., USA, in Healthy, Adult, Human Subjects under Fast and Fed Conditions" (24-VIN-0036), which was deemed safe to proceed bythe Agency. Refer to Safe to Proceed letter in DARRTS dated August 15, 2024.

On November 22, 2024, the Applicant submitted an Initial Pediatric Study Plan to the Agency, and an Agreed Initial Pediatric Study Plan letter was issued by the Agency on April 25, 2025. The Agency agreed with the Applicant' s proposal for no additional studies, or waivers for their drug product, since the listed drug (i.e., desmopressin acetated oral tablet) was considered fully assessed and labeled for pediatric patients with central diabetes insipidus. However, the Agreed Pediatric Study Plan included a specification for the Applicant to provide a complete safety evaluation of excipients used in the formulation of the drug product in pediatric patients, including neonates, in the context of the known presence of benzoic acid and its derivatives as excipients of the drug product.

On April 16, 2025, the Applicant submitted the Assessment of Excipients report under IND 172488 (SD #6).

On April 25, 2025, the Applicant submitted a NDA for Desmopressin Acetate Oral Solution 0.05 mg/mL under section 505(b)(2) of the of the Federal Food, Drug, and Cosmetic (FD&C) Act for the treatment of central diabetes insipidus, relying upon the Agency's findings of safety and effectiveness of the listed drug (LD) DDAVP (desmopressin acetate) oral tablets (NDA 019955, approved September 6, 1995).

# 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) performed a clinical inspection of Trial 24-VIN-0036, which was conducted by Axay Parth at Veeda Clinical Research Pvt., Ltd., Mehsana, Gujarat, India. OSIS concluded that "based on the inspection findings, there are no identified concerns for Veeda Clinical Research Pvt., Ltd. regarding reliability of the data and human subject protection for inspected study 24-VIN-0036 for the review division consideration." Refer to the OSIS consult report in DARRTS dated December 12, 2025, for details.

## 4.2. Product Quality

Desmopressin Acetate Oral Solution, 0.05 mg/mL, is a colorless to slightly yellow, clear solution. The drug product contains 0.05 mg/mL desmopressin acetate as the active pharmaceutical ingredient (API), benzoic acid (b) (4) mg/mL) and sodium benzoate (b) (4) mg/mL) serving dual functions as antimicrobial preservatives and buffering agents (b) (4) of the drug product solution as 4.8 to 5.2, and purified water (b) (4). The product is packaged in 150-mL amber (b) (4) glass (type III) containers with (b) (4) closures, and has a fill volume of 145 mL.

*Drug Product*
The Office of Pharmaceutical Quality (OPQ) review team has determined that the drug product is adequate and recommends approval.

As outlined in the review, the Applicant has provided results for extractable studies and leachable studies for three time points at 0, 12 and 23 months in upright and inverted orientation. No volatile, semi-volatile, nonvolatile compounds were found above the antimicrobial effectiveness testing (AET) and no inorganic leachables were found above the limit of quantitation. This confirms that the proposed container closure system is suitable for desmopressin acetate 0.05 mg/mL drug product for the proposed shelf-life of 24 months. The drug product specifications (for release and shelf-life) include tests for description, identification, assay, preservatives (reported as total benzoic acid), pH, density, degradation products, microbial content, and deliverable volume. The proposed individual tests and their acceptance criteria in the drug product specifications are aligned with the general principles outlined in section 3.2.2 universal tests and section 3.3.2.2 tests for oral liquids in FDA Guidance for Industry for ICH Q6A, and the justification for specifications is adequate. The analytical procedures used for testing the drug product are supported by validation studies. These analytical methods for assay, degradation products, and preservatives are stability-indicating testing methods, as verified by the forced degradation studies.

As outlined in the OPQ review, the Applicant has manufactured three registration batches at commercial scale ( (b) (4) /kg, approximately (b) (4) containers of the finished drug product). The submitted batch release analyses reveal that these batches meet the specifications. The Applicant has provided the following stability data from these three batches: 18-month data under long-term storage conditions (25°C ± 2°C / 60% ± 5% RH), 18-month data under refrigerated conditions (5°C ± 3°C),12-month data under intermediate conditions (30°C ± 2°C / 65% ± 5% RH), and 6-month data under accelerated conditions (40°C ± 2°C / 75% ± 5% RH), which reveal no stability trend and no out of specification event at any tested timepoints.

As per OPQ review, the Applicant has also provided results for in-use stability for 120 days as per in-use time recommended on the product container label. Based on the provided stability data and the principle of FDA Guidance for Industry for ICH Q1E, a 24-month expiration period can be granted for the drug product Desmopressin Acetate Oral Solution, 0.05 mg/mL, to be stored at 2°C to 25°C (36°F to 77°F) with excursions permitted to 30°C (86°F), must not be frozen, and should be used within 120 days after opening.

Refer to the Drug Product Quality review by Dr. Lotika Bajaj from February 2, 2026, for details.

*Drug Substance*
The Office of Pharmaceutical Quality (OPQ) review team has determined that the drug product is adequate and recommends approval.

According to the review, the Applicant cross-reference the information on the drug substance, desmopressin acetate to Type II DMF 023676. A Letter of Authorization was provided by the Applicant in support of this NDA. OPQ team reviewed the DMF and found it adequate to support this application. There is no new amendment since the last review (9/7/2021, R05_AQ). According to the OPQ review, PolyPeptide Laboratories is responsible for the manufacture, release, and stability testing of the drug substance used in the drug product, Desmopressin Acetate Oral Solution, 0.05 mg/mL. Particle size and polymorphism of the drug substance are not critical quality attributes because the drug product in this NDA is a solution.

Refer to the Drug Substance Quality review by Mitchell McCloskey from January 5, 2026, for details.

*Manufacturing*
The Office of Pharmaceutical Manufacturing Assessment (OPMQ) review team has determined that the drug substance and the drug product manufacturing facilities, as well as the analytical laboratories, are acceptable and recommend approval. Refer to Manufacturing Quality review by Chaoying Ma from November 20, 2025, for details.

*Environmental Assessment*
The Applicant claims that this NDA qualifies for a categorical exclusion from the requirement for an anronmental assessment because approval of the NDA would not increase the use of the

active moiety, desmopressin acetate (21 CFR 25.31(a). The Office of Pharmaceutical Quality review team agreed with with assessment.

## 4.3. Clinical Microbiology

The microbiology reviewer found the drug product adequate in all assessed areas with no deficiencies identified. The preservative system effectively maintains microbial quality, stability data support the proposed expiration period, and in-use testing confirms the product remains microbiologically safe throughout its intended use period.

Refer to the Microbiology review by Dr. Aditi Das from August 20, 2025, for details.

## 4.4. Devices and Companion Diagnostic Issues

Not applicable.

# 5 Nonclinical Pharmacology/Toxicology

No pharmacology/toxicology data were submitted with the current application nor were any data required.

# 6 Clinical Pharmacology

## 6.1. Executive Summary

The Applicant submitted NDA 219873 to seek approval of the desmopressin acetate oral solution (0.05 mg/mL) via the 505(b)(2) regulatory pathway for the following indication:

- Antidiuretic replacement therapy for patients 2 years of age and older in the management of central diabetes insipidus [redacted (b) (4)]. <DRUG PRODUCT> is ineffective for the treatment of nephrogenic diabetes insipidus.

The listed drug (LD) is DDAVP (desmopressin acetate) Oral Tablets (NDA 019955).
The Applicant conducted the following clinical study (24-VIN-0036) under NDA 219873:

- An Open Label, Balanced, Randomized, Single-Dose, Three-Treatment, Three-Sequence, Three-Period, Three-way Crossover Oral Bioequivalence Study of Desmopressin Acetate Oral Solution, 0.05 mg/mL (at Dose of 0.6 mg/12 mL) of Eton Pharmaceuticals, Inc., USA comparing with that of DDAVP® Tablets (desmopressin acetate) 0.2 mg [at dose of 0.6 mg (0.2 mg X 3 Tablets)] of Ferring Pharmaceuticals Inc., USA, in Healthy, Adult, Human Subjects under Fast and Fed Conditions.

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data for NDA 219873 and finds the data acceptable and recommends approval.

## 6.2. Summary of Clinical Pharmacology Assessment

The Applicant conducted one study, 24-VIN-0036, as a comparative pharmacokinetic (PK) study, to establish a scientific bridge to the listed drug. Bioequivalence between desmopressin acetate oral solution and the listed drug DDAVP (desmopressin acetate) Oral Tablets was achieved for AUC and Cmax under the fasted state. In addition, the effect of food on the PK of desmopressin acetate oral solution was observed. To be specific, desmopressin Cmax was decreased by 72% and the AUC was decreased by 64% following administration with a high-fat meal (1000 calories, 50% fat). The Applicant proposed that desmopressin acetate oral solution should be taken only on an empty stomach (1 hour before or 2 hours after a meal). Overall, data from the fasting bioequivalence study support adequate bridging between desmopressin acetate oral solution and the listed drug DDAVP (desmopressin acetate) Oral Tablets.
The reviewer's conclusions from the study agree with those of the Applicant and are discussed in Section 6.3.

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

*Mechanism of Action*
Desmopressin acetate's primary pharmacodynamic action involves its binding to V2 receptors (vasopressin receptor type 2). V2 receptors are primarily located in the distal convoluted tubule and collecting ducts of the nephron in the kidneys. These receptors play a crucial role in

regulating water reabsorption and urine concentration. By influencing the permeability of the renal tubules, V2 receptors help maintain the body's water balance and overall homeostasis.

*Absorption*
The bioavailability of desmopressin following oral administration is about 5% compared to intranasal formulation, and about 0.16% compared to intravenous formulation.

*Effect of Food*
Desmopressin Cmax was decreased by 72% and the AUC was decreased by 64% following administration with a high-fat meal (1000 calories, 50% fat).

*Distribution*
Desmopressin mean apparent (oral) volume of distribution (SD) is 11717 (5086) L.

*Elimination*
Desmopressin is mainly excreted in the urine. Desmopressin estimated elimination half-life is 3.6 hours. Desmopressin mean apparent (oral) clearance (SD) is 2264 (940) L/hr.

*Renal Impairment*
Terminal half-life significantly increased from 3 hours in normal healthy patients to 9 hours in patients with severe renal impairment.

### 6.2.2. General Dosing and Therapeutic Individualization

**General Dosing**

- Recommended starting dose is 0.05 mg twice daily and should be individually adjusted to the optimum therapeutic dose. The usual dosage range is 0.1 mg daily to 1.2 mg daily orally divided into two or three daily doses.
- The dosage of desmopressin acetate oral solution must be determined for each individual patient and adjusted according to the diurnal pattern response estimated by adequate duration of sleep and adequate water turnover.
- Desmopressin acetate oral solution should be taken only on an empty stomach (1 hour before or 2 hours after a meal).

**Therapeutic Individualization**

Same as the listed drug

**Outstanding Issues**

None

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

To support the safety and efficacy of desmopressin acetate oral solution, the Applicant provided a clinical PK study (24-VIN-0036) to establish a bridge between this proposed product and the listed drug DDAVP® oral tablet.

Study design

This study was an open label, balanced, randomized, single-dose, three-treatment, three-sequence, three-period, three-way crossover oral bioequivalence study in healthy adult subjects under fasted and fed conditions. This study was conducted to characterize the pharmacokinetic profile of the proposed product in comparison to the reference product after single oral dose administration under the fasted condition, as well as to evaluate the food effect of the test product. Both test and reference product were administered at a dose of 0.6 mg, i.e., three tablets of the reference product (R) (0.2 mg × 3 Tablets) or 12 mL of the test product (T) (0.05 mg/mL× 12 mL). Subjects were fasted overnight from at least 10.00 hours before schedule time of dosing. For Test product (TFE) arm, the subjects received breakfast consisting of high-fat and high-calories (approximately 800-1000 calories) 30 minutes prior to dosing for Test product (TFE). The subjects were instructed to finish the breakfast within 30 minutes before the scheduled dosing time. The subjects received a standard meal at about 4.00, 8.00 and 12.00 hours after dosing in each period. Drinking water was not allowed from two hours before dosing until eight hours after dosing (except 240 ± 2mL water was provided to each subject at time of dosing and/or lunch).
The administration of each product was followed by a sufficiently long period of time to ensure complete elimination of the drug (washout period) before the next administration. A washout period of fourteen (14) days was maintained between each consecutive dosing day in the study and were sufficient for complete elimination of the administered drug from the body (the plasma half-life of desmopressin acetate is 1.5 to 2.5 hours).

Study results

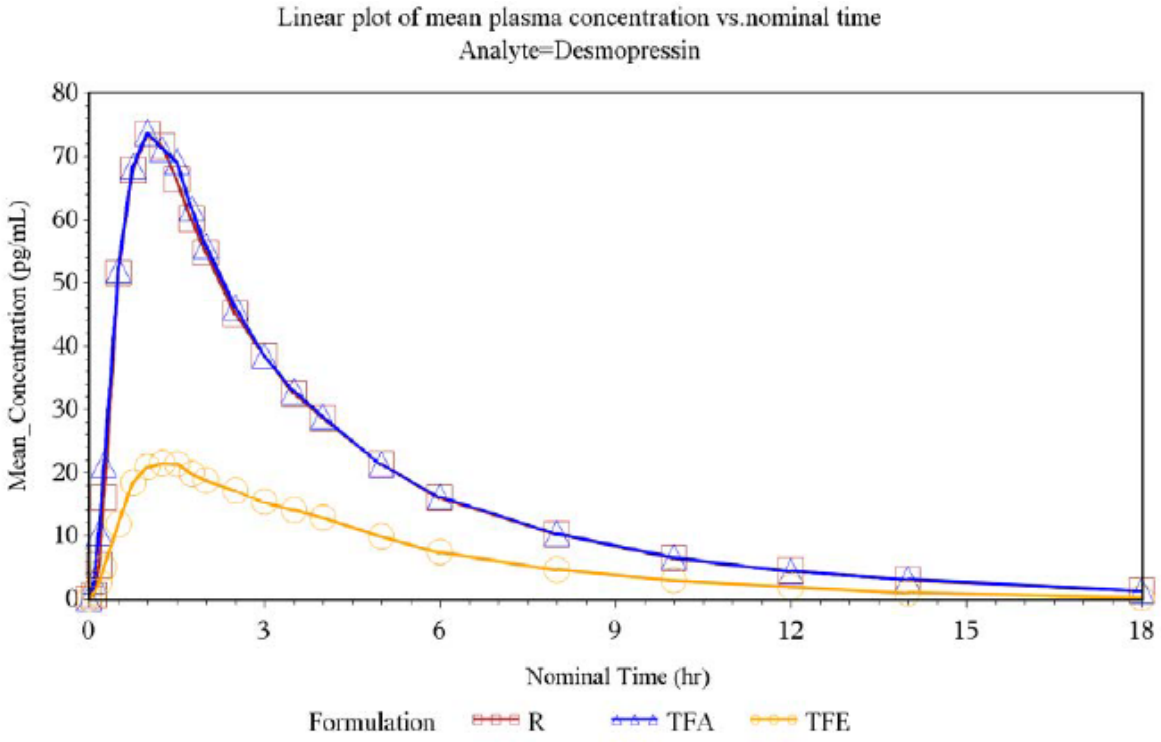
Seventy five (75) subjects were initially enrolled into the study as per plan. Pharmacokinetic analysis was performed over 73 subjects who completed at least two study periods with respect to the comparison of (TFA vs. R) & (TFE vs. TFA). The pharmacokinetic parameters $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $T_{max}$, $t_{1/2}$, $K_{el}$ and AUC_%Extrap_obs were calculated for desmopressin using plasma concentration vs. time profile data in individual subjects who complete at least two study periods with respect to the comparison of (TFA vs. R) & (TFE vs. TFA) was shown in Table 3. Linear plots of mean plasma concentrations versus time for Reference (R) and Test (TFA and TFE) formulations are presented in Figure 1.

**Table 3. The Measured Pharmacokinetic Parameters of Desmopressin under the Fasting Condition.**

| Pharmacokinetic Parameters (Units) | Arithmetic Mean ± SD (%CV) | |
|---|---|---|
| | Desmopressin acetate oral solution | DDAVP Oral Tablets |
| $C_{max}$ (pg/mL) | 81.821 ± 32.4700 (39.68%) | 82.127 ± 33.0887 (40.29%) |
| $T_{max}$ (hr) | 1.000 (0.500 - 1.750) | 1.000 (0.500 - 2.000) |
| $AUC_{0-t}$ (hr*pg/mL) | 303.837 ± 133.7376 (44.02%) | 309.303 ± 134.7488 (43.57%) |
| $AUC_{0-\infty}$ (hr*pg/mL) | 313.873 ± 137.5065 (43.81%) | 3.628 ± 0.7777 (21.44%) |
| $t_{½}$ (hr) | 3.650 ± 0.7760 (21.26%) | 3.187 ± 0.6029 (18.92%) |
| $K_{el}$ (1/hr) | 0.19772 ± 0.038446 (19.44%) | 0.19872 ± 0.037741 (18.99%) |
| $AUC_{_\%Extrap_obs}$ (%) | 3.353 ± 1.1879 (35.43%) | 3.394 ± 1.3806 (40.68%) |
| Apparent Vd (L) | 1172 ± 509 | 1193 ± 521 |
| Apparent CL (L/hr) | 2264 ± 940 | 2348 ± 1052 |

*Source: Table 21, pages 59-60, 24-VIN-0036 CSR and Table 1, page 1, Response to Information Request submited on November 20, 2025.*

**Figure 1. Linear Plot of Mean Plasma Concentration vs Nominal Time Profile.**




*Source: Figure 3, page 60, 24-VIN-0036 CSR.*

The geometric least squares mean of Test Formulation (T) (TFE and TFA) and Reference Formulation (R), its ratio (TFA Vs R and TFE Vs TFA), power, intra-subject variability and 90% confidence intervals the Geometric least square mean ratio (TFA Vs R and TFE Vs TFA) obtained from the analysis of ln-transformed parameters Cmax, AUC0-t and AUC0-∞ are summarized in Table 4.

**Table 4. The Statistical Results for Primary Pharmacokinetic Parameters of Desmopressin for TFA vs R.**

| Parameters (Units) | Geometric Least Squares Means and its ratio (N = 71) | | | Intra subject %CV | 90% Confidence Interval | Power (%) |
|---|---|---|---|---|---|---|
| | Test Product ($T_{FA}$) | Reference Product (R) | Ratio ($T_{FA}$/R) (%) | | | |
| $C_{max}$ (pg/mL) | 77.300 | 75.865 | 101.89 | 29.68 | 93.92% - 110.54% | 98.17 |
| $AUC_{0-t}$ (hr*pg/mL) | 282.146 | 271.968 | 103.74 | 32.91 | 94.83% - 113.50% | 95.99 |
| $AUC_{0-\infty}$ (hr*pg/mL) | 291.833 | 281.523 | 103.66 | 32.39 | 94.88% - 113.26% | 96.41 |

*Source: Table 2, page 62, 24-VIN-0036 CSR.*

The statistically significant difference between median of $T_{max}$ of both formulations were evaluated using Non-parametric Wilcoxon signed rank test. In this study, P-Value was observed as 0.8214 (>0.05), which is statistically non-significant. The 95% confidence interval were calculated and observed ((0.000 %) - (0.00 %)) using a non-parametric Wilcoxon signed rank test to compare untransformed values of $T_{max}$.

The 90% confidence intervals for the ratio of test/reference geometric means for both Cmax and AUC fall within 80.00% - 125.00%. Therefore, the test product (Desmopressin Acetate Oral Solution, 0.05 mg/mL) when compared with the Reference Product (R) (DDAVP® Tablets (desmopressin acetate) 0.2 mg) meets the bioequivalence criteria in terms of rate (Cmax) and extent (AUC) of absorption under fasting conditions. See Section 6.3.2 for detailed discussion for the food effect of the test product.

### 6.3.2. Clinical Pharmacology Questions

**Does the clinical pharmacology program provide supportive evidence of effectiveness?**

Yes, the Applicant conducted the Study 24-VIN-0036 to support the approval of the proposed product. The PK study compared the relative bioavailability between the proposed product desmopressin acetate oral solution and the listed drug DDAVP Oral Tablets under the fasting condition. The results from Study 24-VIN-0036 supported the use of Clinical Pharmacology information of the DDAVP Oral Tablets labeling to be used for the labeling of this product. In addition, the food effect of desmopressin acetate oral solution was also investigated in Study 24-VIN-0036.
The reviewer's conclusions of the studie agrees with that of the Applicant and are discussed in Section 6.3.1.

**Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

Yes. See detailed rationale under section 6.3.2.

**Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

Same as the listed drug

**Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

The effect of a high-fat and high-calorie meal on the rate and extent of desmopressin absorption following a single oral dose of 0.6 mg Desmopressin Acetate Oral Solution in healthy subjects was evaluated in Study 24-VIN-0036. Ingestion of Desmopressin Acetate Oral Solution with a high-fat and high-calorie meal resulted in a 72% and 64% reduction in Cmax and AUC, respectively (Table 5). The terminal $t_{1/2}$ (~3.1-3.5 hours) was similar between the fed and fasted states. The median $T_{max}$ (~1-1.25 hours) was similar in both arms. The Applicant proposed that Desmopressin Acetate Oral Solution should be taken only on an empty stomach (1 hour before or 2 hours after a meal). While the Applicant did not provide any clinical data to support the proposed time interval between drug administration and food intake, the proposed recommendations appear to be scientifically sound and offer practical dosing flexibility for the twice-daily regimen. Considering that desmopressin has a short Tmax (~1-1.25 hours), substantial absorption of desmopressin in the gastrointestinal tract is achieved within the first two hours after dosing. The List drug DDAVP oral tablet was also reported with significant food effect. However, there is no restriction of food intake in the label likely because no effect on dynamics (urine production or osmolality) was observed. Therefore, the labeling recommendation is that “Desmopressin Acetate Oral Solution should be taken only on an empty stomach (at least 1 hour before or 2 hours after a meal)”.

**Table 5. The Measured Pharmacokinetic Parameters of Desmopressin under Fasting and Fed Conditions Following a Single dose of Desmopressin Acetate Oral Solution at 0.6 mg.**

| Pharmacokinetic Parameters (Units) | Arithmetic Mean ± SD (%CV) | |
|---|---|---|
| | Fasting condition | Fed condition |
| $C_{max}$ (pg/mL) | 81.821 ± 32.4700 (39.68%) | 23.576 ± 12.9643 (54.99%) |
| $T_{max}$ (hr) | 1.000 (0.500 - 1.750) | 1.250 (0.250 - 4.000) |
| $AUC_{0-t}$ (hr*pg/mL) | 303.837 ± 133.7376 (44.02%) | 110.573 ± 61.3270 (55.46%) |
| $AUC_{0-\infty}$ (hr*pg/mL) | 313.873 ± 137.5065 (43.81%) | 117.025 ± 62.0752 (53.04%) |
| $t_{½}$ (hr) | 3.650 ± 0.7760 (21.26%) | 3.187 ± 0.6029 (18.92%) |
| $K_{el}$ (1/hr) | 0.19772 ± 0.038446 (19.44%) | 0.22418 ± 0.037049 (16.53%) |
| $AUC_{_\%Extrap_obs}$ (%) | 3.353 ± 1.1879 (35.43%) | 6.392 ± 3.1776 (49.71%) |

*Source: Table 21, page 59, 24-VIN-0036 CSR.*

**Question on clinically relevant specifications (TBD)?**

None.

**Office of Study Integrity and Surveillance (OSIS) inspection**

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study 24-VIN-0036 (NDA 219873, Desmopressin Acetate Oral Solution 0.05 mg/mL) conducted by Axay Parth at Veeda Clinical Research Pvt., Ltd., Mehsana, Gujarat, India. Based on the review in DARRTS dated Decemver 12 2025 (Reference ID: 5710883), "Form FDA 483 was not issued at the inspection close-out. There were no discussion items. Based on the inspection findings, there are no identified concerns for Veeda Clinical Research Pvt., Ltd. regarding reliability of the data and human subject protection for inspected study 24-VIN-0036 for the review division consideration."

OSIS determined that an inspection of (b) (4), the bioanalytical site for study 24-VIN-0036 (NDA 219873, Desmopressin Acetate Oral Solution 0.05 mg/mL) is not needed, as OSIS conducted an inspection for this analytical site in (b) (4).

# 7 Sources of Clinical Data and Review Strategy

## 7.1. Table of Clinical Studies

**Table 6. Listing of Clinical Trials Relevant to this NDA**

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| BE | 24-VIN-0036 | 5.3.1.2 | The objectives of this study were to<br>• evaluate and compare the single-dose oral bioequivalence of Desmopressin Acetate Oral Solution, 0.05 mg/mL (at a dose of 0.6 mg/12 mL) and DDAVP® Tablets (desmopressin acetate), 0.2 mg (0.2 mg x 3 tablets) in healthy, adult, human subjects under fed and fasting conditions.<br>• monitor the safety and tolerability of a single dose of Desmopressin Acetate Oral Solution, 0.05 mg/mL.<br>• assess the effect of food on the bioavailability of Desmopressin Acetate Oral Solution, 0.05 mg/mL after a single dose in healthy, adult, human subjects under fed vs. fasting conditions | Open-label, single-dose, randomized, three-treatment, three-sequence, three-period, three-way crossover, bioequivalence, study | Desmopressin Acetate Oral Solution, 0.05 mg/mL; 0.2 mg Dose; Oral | Completed the study as per protocol: 73<br><br>Included in safety analyses: 73<br><br>Included in bioanalysis: 75<br><br>Included in the PK analysis: 73<br><br>Included in the statistical analysis:<br>Desmopressin Acetate Oral Solution vs. DDAVP fasted: 71<br>Desmopressin Acetate Oral Solution fasted vs. fed: 70 | Healthy subjects | Single oral dose in each of the three periods with a 14-day washout between drug administrations. | Complete; Full Report |

*Source: Tabular Listing of All Clinical Studies submitted by the Applicant, Module 2.5 Clinical Overview*

### 7.2. Review Strategy

The Applicant submitted one BE trial (24-VIN-0036) to establish the bioequivalence between Desmopressin Acetate Oral Solution and DDAVP tablet after a single oral dose administration of 0.6 mg under fasting and fed conditions. Refer to Table 6. The trial design and pharmacokinetic results are described in Section 6.3 above. The safety results are described in Section 8.2 below.

## 8 Statistical and Clinical and Evaluation

### 8.1. Review of Relevant Individual Trials Used to Support Efficacy

No clinical trials were conducted to evaluate the efficacy of the drug product.

### 8.2. Review of Safety

#### 8.2.1. Safety Review Approach

The Applicant has submitted one BE trial in the current submission. Trial 24-VIN-0036 established the bioequivalence of desmopressin acetate oral solution against DDAVP (desmopressin acetate) oral tablet, after a single oral dose of 0.6 mg. This trial enrolled healthy, adult subjects.

#### 8.2.2. Review of the Safety Database

**Overall Exposure**

A total of 75 healthy adult subjects were enrolled in the trial, of whom 73 (97.3%) subjects each received one dose of desmopressin acetate oral solution under fasting condition (Test FA), one dose of desmopressin acetate oral solution under fed condition (Test FE) and one dose of DDAVP oral tablets (Reference).

**Adequacy of the Safety Database:**

The safety of desmopressin acetate oral solution in patients with diabetes insipidus relies on the established safety profile of the reference product, DDAVP tablets.
The safety data included with this application provide data from healthy adults after single dose administration to establish the bioequivalence between desmopressin acetate oral solution and DDAVP tablet. Therefore, these data only provide supportive evidence of safety for this drug product in patients with diabetes insipidus.

#### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

The Applicant's clinical safety assessments were adequate. Subjects were confined to the clinical research facility for at least 10 hours prior to drug administration and until 24 hours

post-dose in each study period. A washout period of 14 days was maintained between each consecutive study periods (between Period 1 and 2, and between Periods 2 and 3). Safety assessments included clinical examination, vital signs measurements, electrocardiograms (ECG), clinical laboratory tests [serum electrolyte (Na, K, Cl), biochemistry, hematology], pregnancy test, and recording of adverse events.

**Issues Regarding Data Integrity and Submission Quality**

None

**Categorization of Adverse Events**

The Applicant's definitions of adverse events (AE) and serious adverse events (SAEs) in the protocol were acceptable. AEs were defined as 'any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporarily associated with the use of a medicinal product, whether or not related to the investigational product.' SAEs were defined as an AE that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event that may have jeopardized the subject or may have required intervention to prevent one of the other outcomes listed above.

**Routine Clinical Tests**

Routine clinical laboratory tests, including biochemistry, and hematology, were obtained at pre-specified time points during the trial. Because of the expected physiologic effect of the desmopressin on electrolytes (i..e, sodium lowering, potassium increase), serum electrolyetes (NA, K, Cl) were closely monitored during the trial , i..e, on the day of each admission and post-dose at 4, 8, 12, 16, 20 and 24 hours in each study period.

### 8.2.4. Safety Results

**Deaths**

No deaths were reported during the trial.

**Serious Adverse Events**

No SAEs were reported during the trial.

**Dropouts and/or Discontinuations Due to Adverse Effects**

Three subjects discontinued the study drug during the trial due to an AE: 2 subjects (both when treated with the Reference product) due to hyponatremia and one subject due to vomiting (when treated with the Test product under fasting condition, Test FA). All 3 AEs were mild or

moderate in severity and they resolved in all 3 subjects. The sodium level in the 2 subjects experiencing hyponatremia was 120 mEq/ml and 127 mEq/ml, respectively. Hyponatremia is an expected pharmacologic effect of the study drug.

**Significant Adverse Events**

There were no severe AEs reported during the trial.

**Treatment Emergent Adverse Events**

A total of 6 subjects reported 6 AEs during the trial, of which 3 AEs (i.e., vomiting, decreased hemoglobin and increased white blood cell count) occurred after treatment with Test product under fasting condition (Test FA), 2 AEs of hyponatremia occurred after treatment with Reference product, and one AE of thrombophlebitis occurred after treatment with Test product under fed condition (Test FE) (Table 7**)**. All AEs were mild, or moderate in severity and were recorded as resolved. The AEs of hyponatremia and vomiting were deemed likely related to study drug, while theremaing AEs of decrease hemoglobin, increased white blood cell count and thrombophlebitis were unlikely to be related to study drug.

**Table 7. Summary of Adverse Events by Preferred Term, Trial 24-VIN-0036**

| | **Reference N = 73 n (%)** | **Test FA N = 73 n (%)** | **Test FE N = 73 n (%)** |
|---|---|---|---|
| Any AE | 2 (2.7) | 3 () | |
| Decreased sodium | 2 (2.7) | 0 | 0 |
| Vomiting | 0 | 1 (1.4) | 0 |
| Decreased hemoglobin | 0 | 1 (1.4) | 0 |
| Increased white blood cell count | 0 | 1 (1.4) | 0 |
| Thrombophlebitis | 0 | 0 | 1 (1.4) |

*N= total number of subjects exposed to treatment; n = number of subjects with AE; %: percent of subjects with AE.*
*MedDRA Preferred Term Version 27.1*
*Source: adae.xpt, JMP version 18, Trial 24-VIN-0036*

Overall, the incidence of AEs in the trial was low and the safety results were consistent with the known safety profile of desmopressin.

**Laboratory Findings**

Except for the AEs of hyponatremia ( n = 2), increased white blood cell count (n=1) and dcreased hemoglobin (n = 1) (Refer to **Treatment Emergent Adverse Events** Section above), there were no other clinical significant laboratory abnormalities during the trial.

**Vital Signs**

No clinically significant abnormalities with respect to vital signs were observed during the trial.

**Electrocardiograms (ECGs)**

Not applicable. Electrocardiogram was not evaluated routinely during the trial.

**Immunogenicity**

Not applicable.

### 8.2.5. Analysis of Submission-Specific Safety Issues

Safety of benzoic acid content in the pediatric population:
During the review of the iPSP (under IND 172488) for the drug product, the Department of Pediatrics and Maternal Health (DPMH) identified the content of benzoic acid and sodium benzoate excipients as a potential safety concern in neonates and infants with central diabetes insipidus requiring chronic daily therapy with this product. Therefore, the Agency requested the Applicant to provide a complete safety evaluation of excipients used in the formulation of the drug product in pediatric patients, including neonates (refer to agreed iPSP correspondence in DARRTS under IND 172488). On April 16, 2025, the Applicant submitted the Assessment of Excipients report under IND 172488 (SD 6). During the NDA review, DGE consulted DPMH to review the Applicant's assessment of the aforementioned safety report to support approval of the drug product in the proposed pediatric population.

According to the DPMH review, the Applicant's risk assessment to address the safety of the benzoic acid excipient content of Desmopressin Acetate Oral Solution used a novel approach relying on estimated permitted daily exposures (PDE) of both excipients based on the known no observed adverse event level (NOAEL) from literature data to support the safety of the proposed product containing both excipients for use in patients from birth to less than 17 years of age. DPMH noted that Applicant's assumption about the true NOAEL for benzyl alcohol and its derivatives, benzoic acid and sodium benzoate, could be flawed, because the rate at which benzyl alcohol is converted to its metabolites cannot be reliably predicted, and thus it would be challenging to make any determination regarding the safety of benzoic acid after administration of benzyl alcohol.

However, DMPH used a different framework to evaluate the safety of benzyl alcohol excipient for Desmopressin Acetate Oral Solution in pediatric patients. This framework is based on estimating the maximum daily dose (MDD) of the excipient expected to be administered to pediatric patients based on the maximum proposed or recommended dosage of the active ingredient(s) within the investigational product. DPMH then determined if the estimated MDD for the excipient in question was associated with known toxicity based on available nonclinical and clinical data. Using this framework, DPMH estimated that the MDD of the total benzoate

dose that would be expected to be administered to a late preterm neonate born at 34-week gestational age would be would be (b) (4) mg/kg/day and (b) (4) mg /kg/day for a pre-term and full term neonate, respectively.

DPMH concluded that in the absence of published reports of benzyl alcohol and benzoate toxicities in pediatric patients in settings other than with high-dose IV benzyl alcohol administration to the pre-term neonatal subpopulation of very low birth weight in whom benzyl alcohol was found to be toxic, oral administration of the amount of benzoate in the microgram range, as it is the case with the current product, is unlikely to pose a safety risk in pediatric patients, including neonates. Furthermore, the likelihood of this product being administered to neonates, the pediatric subpopulation potentially at greatest risk for toxicity when given much higher doses of benzyl alcohol IV, is low, given that central diabetes insipidus is rare during the neonatal period and clinically manifests at least several weeks after birth. Thus, DPMH concluded that the total benzoate excipient content of Desmopressin Acetate Oral Solution should not be the basis for precluding approval of this product down to birth.

Refer to Dr. Ndidi Nwokorie's review in DARRTS, dated February 24, 2026, for details.

### 8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

### 8.2.7. Safety Analyses by Demographic Subgroups

Not applicable.

### 8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

### 8.2.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

Not applicable.

**Human Reproduction and Pregnancy**

Not applicable.

**Pediatrics and Assessment of Effects on Growth**

Not applicable.

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Not applicable.

### 8.2.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

Not applicable.

**Expectations on Safety in the Postmarket Setting**

Not applicable.

### 8.2.11. Integrated Assessment of Safety

Overall, the incidence of AE reported during trial 24-VIN-0036 was low. A total of 6 subjects reported 6 AEs during the trial, of which 3 AEs (i.e., vomiting, decreased hemoglobin and increased white blood cell count) occurred after treatment with Test product under fasting condition (Test FA), 2 AEs of hyponatremia occurred after treatment with Reference product, and one AE of thrombophlebitis occurred after treatment with Test product under fed condition (Test FE). All AEs resolved. There were no deaths, serious or severe AEs reported.

In conclusion, the AEs observed during the trial were consistent with the safety profile of desmopressin, with no new safety findings identified.

## 8.3. Statistical Issues

Not applicable.

## 8.4. Conclusions and Recommendations

Trial 24-VIN-0036 established bioequivalence between desmoressin acetate oral solution and DDAVP tablets under fasting conditions. No new safety findings were observed during this trial, and the safety profile of desmopressin oral solution is favorable. The review team recommends approval of the current NDA.

# 9 Advisory Committee Meeting and Other External Consultations

Not applicable.

# 10 Pediatrics

This application does trigger the Pediatric Research Equity Act (PREA), as the proposed product is for a new dosage form (i.e., oral solution).

On November 22, 2024, the Applicant submitted an Initial Pediatric Study Plan to the Agency, and an Agreed Initial Pediatric Study Plan letter was issued by the Agency on April 25, 2025. The Agency agreed with the Applicant' s proposal for no additional studies, or waivers for their drug product, because the listed drug (i.e., desmopressin acetated oral tablet) was considered fully assessed and labeled for pediatric patients with central diabetes insipidus of all ages.

# 11 Labeling Recommendations

## 11.1. Prescription Drug Labeling

Prescribing information
This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI submitted on April 25, 2025 (Table 8). The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare provider.

The reference product for this application is NDA 019955 DDAVP (desmopressin acetate) tablets with the Prescribing Information in non-PLR format at the time of labeling negotiations and labeling review. No clinical efficacy or safety studies were conducted with DESMODA; therefore, the content of the PI is primarily based on available information from DDAVP tablets and DDAVP injection as applicable.

The reference product DDAVP tablets is approved for the management of central diabetes insipidus (CDI) and primary nocturnal enuresis (PNE). This Applicant stated that they are not seeking approval for the PNE indication in their information request response dated January 16, 2026. Therefore, recommendations related to the PNE indication are not included in this PI.

**Table 8. Key Labeling Changes and Considerations**

| Full PI Sections[1] | Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI |
|---|---|
| BOXED WARNING | None |
| 1 INDICATIONS AND USAGE | • In NDA 019955, the management of CDI is approved for adults and all pediatric patients. At the time of submission, the Applicant proposed an age restriction for pediatric patients aged 2 years and older, based on concerns that the levels of inactive ingredient benzoic acid exceed acceptable levels for the younger pediatric population. The indication statement was revised to include all pediatric patients based on acceptable quantities of benzoic acid. The age limit was removed.<br>• Deleted (b) (4) that are not approved for desmopressin tablets or injection.<br>• Deleted information about (b) (4) as that information should be summarized |

| Full PI Sections[1] | Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI |
|---|---|
| | in Section 14 Clinical Studies.<br>• Limitation of Use subheading was added to clearly convey that DESMODA is not indicated for nephrogenic diabetes insipidus. |
| 2 DOSAGE AND ADMINISTRATION | 2.1 Recommended Dosage for Central Diabetes Insipidus<br>• Created a new subsection and aligned recommendations with DDAVP tablets.<br>• Included recommendations for fluid restriction due to risk of hyponatremia during DESMODA treatment, recommended starting dosage, administration instructions with regard to food intake, and monitoring treatment response for dosage adjustment.<br><br>2.2 Switching Patients with Central Diabetes Insipidus to DESMODA From Desmopressin Acetate Nasal Spray<br>• Created a new subsection to provide recommendation for patients switching to DESMODA who are currently using desmopressin acetate nasal spray. |
| 4 CONTRAINDICATIONS | • Reordered based on public health significance of listed contraindications. |
| 5 WARNINGS AND PRECAUTIONS | 5.1 Hyponatremia<br>• Updated to algin with DDAVP tablets.<br>• Language related to PNE indication are not included.<br><br>5.2 (b) (4) (subsection proposed by the Applicant)<br>• Deleted subsection (b) (4). Recommendation to restrict fluid intake in pediatric and geriatric patients, and monitoring signs and symptoms of hyponatremia are included in Subsection 5.1 Hyponatremia.<br><br>5.2 Fluid Retention<br>• Created a new subsection as it is a clinically important risk with desmopressin acetate.<br>• Language aligned with DDAVP injection.<br><br>5.3 (b) (4) (subsection proposed by the Applicant)<br>• Deleted subsection because (b) (4) Patients (b) (4) are at risk of |

| Full PI Sections[1] | Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI |
|---|---|
| | hyponatremia and is described in Subsection 5.1 Hyponatremia.<br>5.3 Hypersensitivity Reactions<br>• Created a new subsection based on reported cases of serious and fatal cases of anaphylaxis with DDAVP injection and nasal spray.<br><br>5.4 (b) (4) (subsection proposed by the Applicant)<br>• Deleted subsection because the (b) (4) .<br>• Text about use in patients with conditions associated with fluid and electrolyte imbalance are included in Subsection 5.1 Hyponatremia.<br><br>5.4 Risk of Benzyl Alcohol Toxicity in Neonates<br>• Created a new subsection to convey risk of benzyl alcohol toxicity in neonates<br><br>5.5 (b) (4) (subsection proposed by the Applicant)<br>• Deleted subsection because (b) (4) for (b) (4) is not an adverse reaction. |
| 6 ADVERSE REACTIONS | • At the beginning of Section 6, updated the most clinically significant adverse reactions to reflect Section 5 Warnings and Precautions (e.g., hyponatremia, fluid retention, hypersensitivity, and risk of benzyl alcohol toxicity in neonates)<br>• Deleted subheadings (b) (4) proposed by the applicant because the source of the adverse reactions cannot be determined. Adverse reactions are aligned with DDAVP tablets.<br>• Deleted pharmacodynamic and efficacy data from section 6 because they are not adverse reactions. |
| 7 DRUG INTERACTIONS | 7.1 Other Drugs that may Increase Risk of Hyponatremia<br>• Created a new subheading to convey the risk of hyponatremia due to concomitant use of DESMODA and other drugs; content aligned with DDAVP tablets |

| Full PI Sections[1] | Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI |
|---|---|
| | 7.2 Other Vasoconstrictors<br>• Created a new subheading; content aligned with DDAVP tablets |
| 8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment) | 8.1 Pregnancy<br>• Edited subsection based on maternal health review of available information of desmopressin acetate use during pregnancy and animal data.<br>• Added Clinical Considerations/ Disease Associated Maternal and Embryo-Fetal Risk subsection to convey risk associated with untreated CDI during pregnancy.<br>• Edited Animal Data subsection with information in pregnant rats and pregnant rabbits following subcutaneously administration of desmopressin acetate; aligned with DDAVP tablets.<br><br>8.2 Lactation<br>• Edited based on maternal health review of available information of desmopressin use in breastfeeding women.<br><br>8.4 Pediatric Use<br>• Added information about benzoic acid, adverse reactions associated with benzyl alcohol toxicity, and gasping syndrome in neonates.<br><br>8.5 Geriatric Use<br>• Created a new subsection with text aligned with DDAVP tablets<br><br>8.6 Renal Impairment<br>• Created a new subsection with text aligned with DDAVP tablets |
| 9 DRUG ABUSE AND DEPENDENCE | No Applicable |
| 10 OVERDOSAGE | • Minor editorial changes<br>• Deleted (b) (4) because it lacks clinical utility in the management of overdosage. |
| 12 CLINICAL PHARMACOLOGY | 12.2 Pharmacodynamics |

| Full PI Sections[1] | Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI |
|---|---|
| | • Edited to describe the pharmacodynamics following treatment with the DDAVP tablets.<br>• Deleted (b) (4) derived from the bioquivalence study.<br><br>12.3 Pharmacokinetics<br>• Created subheadings Absorption, Distribution, Elimination, and Specific Populations and distributed PK data to appropriate subsections<br>• Added PK data following administration of DESMODA with a high fat meal; information used to support recommendation to take DESMODA on an empty stomach as described in subsection 2.1.<br>• Updated the Renal Impairment subsection with known PK information following administration of DDAVP injection. |
| 13 NONCLINICAL TOXICOLOGY | • Updated to algin with currently available information on DDAVP tablets. |
| 14 CLINICAL STUDIES | • Added support of effectiveness in patients with CDI derived from dose response studies using DDAVP tablets. |
| 17 PATIENT COUNSELING INFORMATION | • Added Administration heading to convey administration instructions outlined in subsection 2.1<br>• Deleted (b) (4) patient counseling information to align with deletions in Section 5. |
| Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) | Section 3 Dosage Forms and Strengths<br>• Minor editorial changes.<br><br>Section 11 Description<br>• Replaced structural formula and molecular weight of desmopressin acetate (anhydrous)<br>• Added solution concentration with the amount of desmopressin acetate and as desmopressin free base.<br>• Added pH of the oral solution.<br><br>Section 16 How Supplied/Storage and Handling<br>• Added dosage form and storage container |

Source: Generated by the Review Team
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): PI, Prescribing Information

Other Prescription Drug Labeling
Upon approval of this NDA, the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Information

# 12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

# 13 Postmarketing Requirements and Commitment

Not applicable.

# 14 Appendices

## 14.1. References

References were included as footnotes throughout the review.

## 14.2. Financial Disclosure

**Table 9: Covered Clinical Study 24-VIN-0036**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 5 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

## 14.3. OCP Appendices (Technical documents supporting OCP recommendations)

A liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method for the estimation of desmopressin in K3EDTA human plasma by SPE extraction technique was developed by (b) (4) This method made use of Turbo Ion Spray (TIS) in Positive mode for Desmopressin using triple quadrupole mass spectrometry where Stable isotope labeled desmopressin D5 was used as internal standards (ISTD). Analyte was separated on Agilent ZORBAX 300SBC18 3.5µm, 4.6 ×100 mm, using 0.1% Acetic Acid in water (v/v): 0.1% Acetic Acid in Acetonitrile (v/v), 80:20 v/v in mobile phase at flow rate of 0.500 mL/min under binary programme. Quantification of desmopressin was performed using multiple-reaction monitoring mode (MRM) where transition of 535.300 \328.200 (m/z), 535.200 \328.200 (m/z), 535.100 \328.200 (m/z) (Drug-TIC) and 537.700 \328.300 (m/z) (m/z) (ISTD) in Positive mode. The summary of bioanalytical method and validation metrics are presented in Table 10. The bioanalytical methods used are adequately validated.

**Table 10. Summary Review of Bioanalytical Methods Measuring Etonogestrel in Human Serum**.

| Parameter | Etonogestrel |
|---|---|
| Bioanalytical method validation report | VIN-BRD-MV-1624 |
| Validation assay range (pg/mL) | 1.056 to 264 |
| QCs (pg/mL) | 1.056, 3.168, 15.84, 100.32, and 200.64 |
| Inter-day precision (% CV) | 2.78 to 5.86 |
| Inter-day accuracy (% Bias) | -2.49 to -0.70 |
| Intra-day precision (% CV) | 1.16 to 9.67 |
| Intra-day accuracy (% Bias) | -4.30 to 3.09 |
| Reference standard | Lot Number: Lot DS-120321 |
| Specificity | No interference observed in the blank matrix (9 samples) |
| Freeze/thaw stability | 5 freeze (-70/-20°C)-thaw (ambient temperature) cycles |
| Bench-top/process stability | 7 hours at wet ice bath below 15 °C |

| | |
|---|---|
| Stability of Extract at Ambient Temperature | 7 hours at Ambient Temperature (25±5°C) in Reconstitution Solution |
| Stability of Extract in Refrigerator | 95 hours at 5±3° in Reconstitution Solution |
| Autosampler Re-Injection Reproducibility | 69 hours at 5±3 °C. |
| Stability of Analyte in Blood | 2 hours at wet ice bath (below 10 °C) with respect to zero hour. |
| Solution Stability | Analyte Stock: 23 hours at ambient temperature (25±5 °C)<br>Analyte Stock: 13 Days at 5±3 °C |
| Long-term storage stability | 177 Days at -20±5°C and 300 Days at -78±8 °C. |
| Dilution Integrity | Dilution Factor: 10 |
| Carryover During Batch Run | % Carryover for Analyte: ≤ 6.74, % Carryover for ISTD: ≤ 0.74 |
| Cross Specificity | The Mean interfering response at the retention time of ISTDs from ULOQ samples: 2.13 % |
| Recovery - Analyte & Internal Standard | % Overall Mean (Grand Mean) Recovery of Analyte with Correction Factor: 87.54<br>% Difference in Recovery of Analyte and ISTD: 85.33 |

Source: Validation Reports VIN-BRD-MV-1624 and VIN-BRD-MV-1624 amendment 1
Abbreviations: CV, coefficient of variation; QC, quality control

Bioanalytical performance for desmopressin

The concentrations of desmopressin were determined in a total of 4809 human serum samples obtained from Study 24-VIN-0036 at (b) (4). Four levels of quality controls were analyzed in each run and the results of precision/accuracy met the preset criteria. The period between first sample collection and last sample analysis was 125 days. The established long-term stability of the samples was 177 Days at -20±5°C and 300 Days at -78±8 °C. Samples were analyzed within established long-term stability. A total of 292 study samples (approximately 10%) were selected for incurred sample reanalysis (ISR). Among them, 92.8% met the predefined criteria of having a difference within ±20% from the initial values.

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