Rev. December 2002

DDAVP®

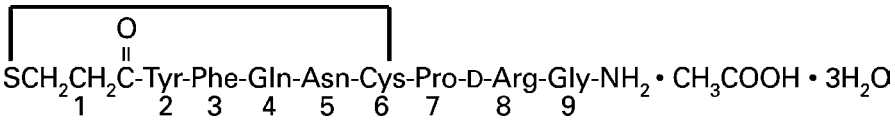
Rhinal Tube

(desmopressin acetate)

DESCRIPTION

DDAVP® Rhinal Tube (desmopressin acetate) is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Mol. wt. 1183.34 Empirical formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$



1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate.

DDAVP Rhinal Tube is provided as an aqueous solution for intranasal use.

Each mL contains:

Desmopressin acetate	0.1 mg
Chlorobutanol	5.0 mg
Sodium Chloride	9.0 mg

Hydrochloric acid to adjust pH to approximately 4

CLINICAL PHARMACOLOGY

DDAVP Rhinal Tube contains as active substance desmopressin acetate, a synthetic analogue of the natural hormone arginine vasopressin. One mL (0.1 mg) of intranasal DDAVP (desmopressin acetate) has an antidiuretic activity of about 400 IU; 10 μg of desmopressin acetate is equivalent to 40 IU.

1. The biphasic half-lives for intranasal DDAVP were 7.8 and 75.5 minutes for the fast and slow phases, compared with 2.5 and 14.5 minutes for lysine vasopressin, another form of the hormone used in this condition. As a result, intranasal DDAVP provides a prompt onset of antidiuretic action with a long duration after each administration.
2. The change in structure of arginine vasopressin to DDAVP has resulted in a decreased vasopressor action and decreased actions on visceral smooth muscle relative to the enhanced antidiuretic activity, so that clinically effective antidiuretic doses are usually below threshold levels for effects on vascular or visceral smooth muscle.
3. DDAVP administered intranasally has an antidiuretic effect about one-tenth that of an equivalent dose administered by injection.

INDICATIONS AND USAGE

Primary Nocturnal Enuresis: DDAVP Rhinal Tube is indicated for the management of primary nocturnal enuresis. It may be used alone or adjunctive to behavioral conditioning or other non-pharmacological intervention. It has been shown to be effective in some cases that are refractory to conventional therapies.

Central Cranial Diabetes Insipidus: DDAVP Rhinal Tube is indicated as antidiuretic replacement therapy in the management of central cranial diabetes insipidus and for management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. It is ineffective for the treatment of nephrogenic diabetes insipidus.

The use of **DDAVP Rhinal Tube** in patients with an established diagnosis will result in a reduction in urinary output with increase in urine osmolality and a decrease in plasma osmolality. This will allow the resumption of a more normal life-style with a decrease in urinary frequency and nocturia.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

Patients are selected for therapy by establishing the diagnosis by means of the water deprivation test, the hypertonic saline infusion test, and/or the response to antidiuretic hormone. Continued response to intranasal DDAVP can be monitored by urine volume and osmolality.

DDAVP is also available as a solution for injection when the intranasal route may be compromised. These situations include nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. Intranasal delivery may also be inappropriate where there is an impaired level of consciousness. In addition, cranial surgical procedures, such as transphenoidal hypophysectomy create situations where an alternative route of administration is needed as in cases of nasal packing or recovery from surgery.

CONTRAINDICATIONS

DDAVP Rhinal Tube is contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of **DDAVP Rhinal Tube**.

WARNINGS

1. For intranasal use only.
2. When DDAVP is administered, in particular, in pediatric and geriatric patients, fluid intake should be adjusted downward in order to decrease the potential occurrence of water intoxication and hyponatremia with accompanying signs and symptoms (headache, nausea/vomiting, decreased serum sodium and weight gain). Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality that may result in seizures which could lead to coma.

PRECAUTIONS

General: Intranasal DDAVP at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with

caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

DDAVP should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia.

Rare severe allergic reactions have been reported with DDAVP. Anaphylaxis has been reported rarely with intravenous and intranasal administration of DDAVP.

Central Cranial Diabetes Insipidus: Since **DDAVP Rhinal Tube** is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case intranasal DDAVP should not be used. For such situations, DDAVP Injection should be considered.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. **DDAVP Rhinal Tube** should be discontinued until the nasal problems resolve.

Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases plasma osmolality measurements may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

Drug Interactions: Although the pressor activity of DDAVP is very low compared to the antidiuretic activity, use of large doses of intranasal DDAVP with other pressor agents should only be done with careful patient monitoring.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with DDAVP have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Pregnancy Category B: Fertility studies have not been done. Teratology studies in rats and rabbits at doses from 0.05 to 10 µg/kg/day (approximately 0.1 times the maximum systemic human exposure in rats and up to 38 times the maximum systemic human exposure in rabbits based on surface area, mg/m^2) revealed no harm to the fetus due to DDAVP. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Several publications of desmopressin acetate's use in the management of diabetes insipidus during pregnancy are available; these include a few anecdotal reports of congenital anomalies and low birth weight babies. However, no causal connection between these events and desmopressin acetate has been established. A fifteen year, Swedish epidemiologic study of the use of desmopressin acetate in pregnant women with diabetes insipidus found the rate of birth defects to be no greater than that in the general population; however the statistical power of this study is low. As opposed to preparations containing natural hormones, desmopressin acetate in antidiuretic doses has no uterotonic action and the physician will have to weigh the therapeutic advantages against the possible risks in each case.

Nursing Mothers: There have been no controlled studies in nursing mothers. A single study in postpartum women demonstrated a marked change in plasma, but little if any change in assayable DDAVP® (desmopressin acetate) in breast milk following an intranasal dose of 10 µg. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DDAVP is administered to a nursing woman.

Pediatric Use: *Primary Nocturnal Enuresis:* **DDAVP Rhinal Tube** (desmopressin acetate) has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) **DDAVP Rhinal Tube** administration has been shown to be safe and modestly effective in pediatric patients aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

Central Cranial Diabetes Insipidus: **DDAVP Rhinal Tube** has been used in pediatric patients with diabetes insipidus. Use in infants and pediatric patients will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS

Infrequently, high dosages of intranasal DDAVP have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	PLACEBO (N=59) %	DDAVP 20 µg (N=60) %	DDAVP 40 µg (N=61) %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

See **WARNINGS** for the possibility of water intoxication and hyponatremia.

OVERDOSAGE

(See **ADVERSE REACTIONS**.) In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for desmopressin acetate or **DDAVP Rhinal Tube**.

An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

DOSAGE AND ADMINISTRATION

Primary Nocturnal Enuresis: Dosage should be adjusted according to the individual. The recommended initial dose for those 6 years of age and older is 20 µg or 0.2 mL solution intranasally at bedtime. Adjustment up to 40 µg is suggested if the patient does not respond.

Some patients may respond to 10 µg and adjustment to that lower dose may be done if the patient has shown a response to 20 µg. It is recommended that one-half of the dose be administered per nostril. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks.

Central Cranial Diabetes Insipidus: This drug is administered into the nose through a soft, flexible plastic rhinal tube which has four graduation marks on it that measure 0.2, 0.15, 0.1 and 0.05 mL. **DDAVP Rhinal Tube** dosage must be determined for each individual patient and adjusted according to the diurnal pattern of response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water turnover. Patients with nasal congestion and blockage have often responded well to intranasal DDAVP. The usual dosage range in adults is 0.1 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. The morning and evening doses should be separately adjusted for an adequate diurnal rhythm of water turnover. For children aged 3 months to 12 years, the usual dosage range is 0.05 to 0.3 mL daily, either as a single dose or divided into two doses. About 1/4 to 1/3 of patients can be controlled by a single daily dose of DDAVP administered intranasally.

HOW SUPPLIED

DDAVP Rhinal Tube is available in a 2.5 mL vial, packaged with two rhinal tube applicators per carton (NDC 0075-2450-01). Also available in a 5.0 mL pump bottle with spray pump delivering 50 doses of 10 µg (NDC 0075-2452-01).

Store refrigerated 2 to 8°C (36 to 46°F). When traveling, closed bottles will maintain stability for 3 weeks when stored at controlled room temperature, 20 to 25°C (68 to 77°F).

Rx Only.

Keep out of the reach of children.

MILITARY: **DDAVP Rhinal Tube,** 1 x 2.5 mL (NSN 6505-01-145-6338).

Manufactured for

Aventis Pharmaceuticals Inc.
Bridgewater, NJ 08807
By Ferring AB, Soldattorpsvägen 5,
SE-200 61 Limhamn, Sweden

US Patent Nos. 5,500,413; 5,596,078; 5,674,850; 5,763,407

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PATIENT INSTRUCTION GUIDE

DDAVP®

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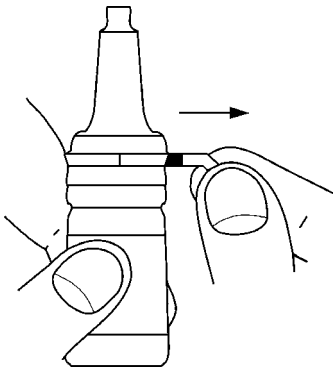
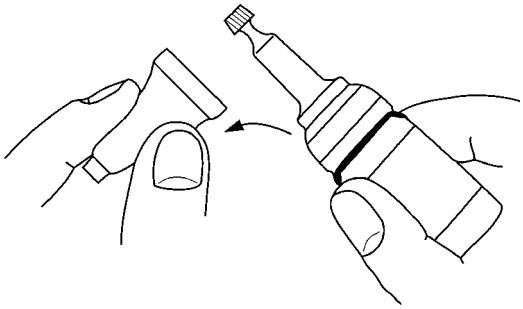
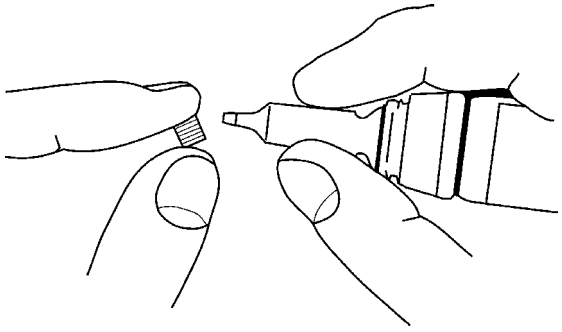
1. Pull plastic tag on neck of bottle.



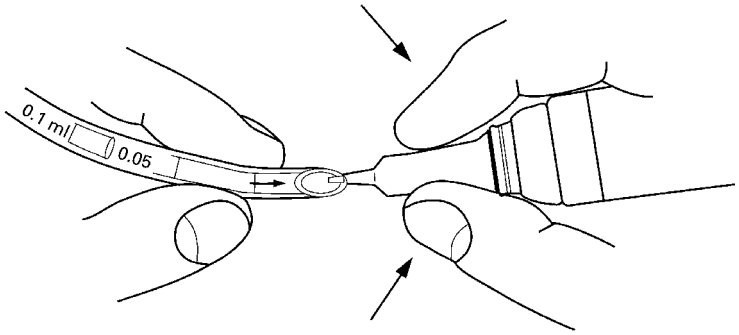
2. Break security seal and remove plastic cap.



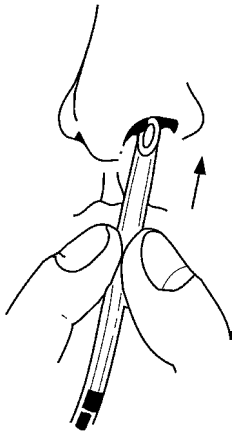
3. Twist off the small knurled seal from the dropper. **Use the same seal reversed to prevent subsequent leakage,** especially if the bottle is not stored upright.



4. The drug is administered by a soft, flexible, plastic rhinal tube which has dose marks at 0.2, 0.15, 0.1 and 0.05 mL. Take the arrow-marked part of the tube in one hand and place the fingers of the other hand around the cylindrical part of the closure. Insert the top of the dropper in a downward position into the arrow-marked end of the tube and squeeze the dropper until the solution has reached the desired calibration mark. The dose is measured from the arrow-marked end of the tube to the appropriate calibration. Disconnect the tube from the bottle by withdrawing the bottle quickly downwards. In order to prevent air bubbles from forming in the tube, maintain constant pressure on the dropper. If difficulty is experienced in filling the tube, a diabetic or tuberculin syringe may be used to draw up the dose and load the tube.

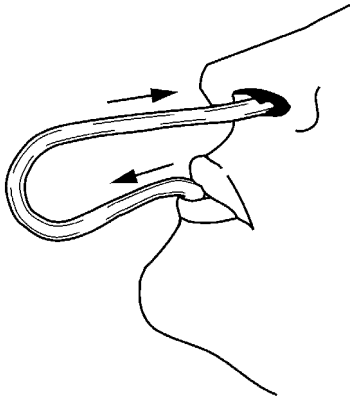


5. Hold the tube with the fingers approximately ¾ inch from the end and insert into a nostril until the tips of the fingers reach the nostril.



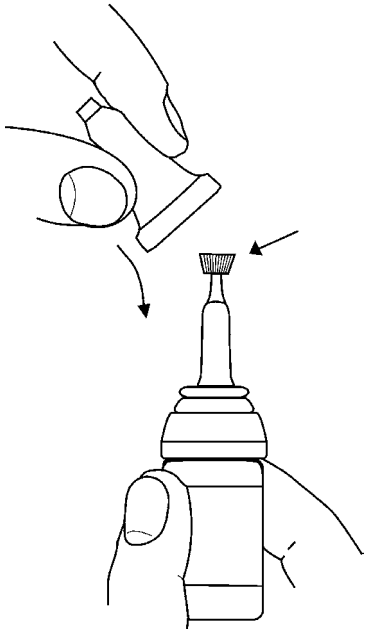
6. Put the other end of the tube into the mouth. Hold the breath, tilt the head back and then blow with a short, strong puff through the tube so that the solution reaches the right place in the nasal cavity. Through this procedure, medication is limited to the nasal cavity and the preparation does not pass down into the throat.

   In very young patients, it may be necessary for an adult to blow the solution into the child's nose. In such cases, the tube will not need to be put into the nose as far as in the older child or adult. The tube should be placed in the nose gently just far enough so that the solution does not run out. A baby must be held firmly and securely.



7. **After use, reseal dropper tip and close the bottle with the plastic cap.** Wash the tube in water and shake thoroughly, until no more water is left. The tube can then be used for the next application.

IMPORTANT:
Replace Knurled Seal



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