Rev. XXXX

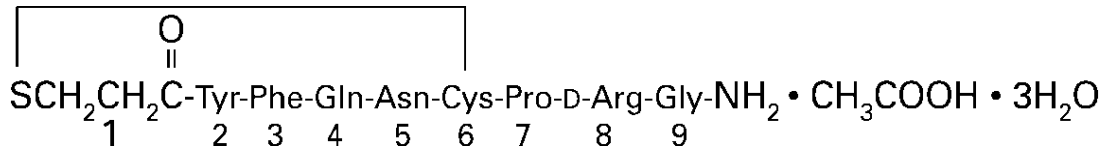
DDAVP®
Nasal Spray
(desmopressin acetate)
Rx only

DESCRIPTION

DDAVP® Nasal Spray (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: $C_{46}H_{64}N_{14}O_{12}S_2 \bullet C_2H_4O_2 \bullet 3H_2O$



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

DDAVP Nasal Spray is provided as an aqueous solution for intranasal use.

Each mL contains:	
Desmopressin acetate	0.1 mg
Sodium Chloride	7.5 mg
Citric acid monohydrate	1.7 mg
Disodium phosphate dihydrate	3.0 mg
Benzalkonium chloride solution (50%)	0.2 mg

The **DDAVP Nasal Spray** compression pump delivers 0.1 mL (10 mcg) of DDAVP (desmopressin acetate) per spray.

CLINICAL PHARMACOLOGY

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

Human Pharmacokinetics: DDAVP is mainly excreted in the urine. A pharmacokinetic study conducted in healthy volunteers and patients with mild, moderate, and severe renal impairment (n=24, 6 subjects in each group) receiving single dose desmopressin acetate (2mcg) injection demonstrated a difference in DDAVP terminal half-life. Terminal half-life significantly increased from 3 hours in normal healthy patients to 9 hours in patients with severe renal impairment.

(See **CONTRAINDICATIONS**.)

INDICATIONS AND USAGE

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

Central Cranial Diabetes Insipidus: DDAVP Nasal Spray 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 Nasal Spray** 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 transsphenoidal hypophysectomy create situations where an alternative route of administration is needed as in cases of nasal packing or recovery from surgery.

CONTRAINDICATIONS

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

DDAVP is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50ml/min).

WARNINGS

1. For intranasal use only.
2. When DDAVP Nasal Spray 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). (See **PRECAUTIONS**, Geriatric Use.) 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 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 Nasal Spray** should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the **DDAVP Nasal Spray** bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

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 mcg/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 (desmopressin acetate). 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 a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg. 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 Nasal Spray** (desmopressin acetate) has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) **DDAVP Nasal Spray** 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 Nasal Spray has been used in children with diabetes insipidus. Use in infants and children 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.

Since the spray cannot deliver less than 0.1 mL (10 mcg), smaller doses should be administered using the rhinal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10 mcg) per dose.

Geriatric Use: Clinical studies of DDAVP Nasal Spray did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. DDAVP is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50ml/min).
(See **CLINICAL PHARMACOLOGY**, Human Pharmacokinetics and **CONTRAINDICATIONS**.)
Use of DDAVP Nasal Spray in geriatric patients will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. (See **WARNINGS**).

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 percentage 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 mcg (N=60) %**	**DDAVP 40 mcg (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 Nasal Spray**.

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 mcg or 0.2 mL solution intranasally at bedtime. It is recommended that one-half of the dose be administered per nostril. Adjustment up to 40 mcg is suggested if the patient does not respond.

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

Central Cranial Diabetes Insipidus: DDAVP Nasal Spray 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.

The nasal spray pump can only deliver doses of 0.1 mL (10 mcg) or multiples of 0.1 mL. If doses other than these are required, the rhinal tube delivery system may be used.

The spray pump must be primed prior to the first use. To prime pump, press down four times. The bottle will now deliver 10 mcg of drug per spray. Discard **DDAVP Nasal Spray** after 50 sprays since the amount delivered thereafter per spray may be substantially less than 10 µg of drug.

Geriatric Use: This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **CLINICAL PHARMACOLOGY**, Human Pharmacokinetics, **CONTRAINDICATIONS**, and **PRECAUTIONS**, Geriatric Use.)

HOW SUPPLIED

DDAVP Nasal Spray is available in a 5-mL bottle with spray pump delivering 50 sprays of 10 mcg (NDC 0075-2452-01). Desmopressin acetate is also available as DDAVP Rhinal Tube, a refrigerated product with 2.5 mL per vial, packaged with two rhinal tube applicators per carton (NDC 0075-2450-01).

Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [see USP]. STORE BOTTLE IN UPRIGHT POSITION.

Keep out of the reach of children.

U.S. Patent Nos. 5,498,598; 5,500,413; 5,596,078; 5,674,850; 5,763,407

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

Rev. XXXX 2004

PATIENT INSTRUCTION GUIDE

DDAVP® Nasal Spray
(desmopressin acetate)

A better way to deliver DDAVP®

Delivering DDAVP® more efficiently
Your doctor has prescribed DDAVP as antidiuretic hormone replacement therapy. Follow the dosage schedule that is specified. The convenient nasal spray pump provides an efficient, reliable way to administer your medication. It is important, however, to adhere completely to the following instructions so that you will always receive a consistent dose of your medication.

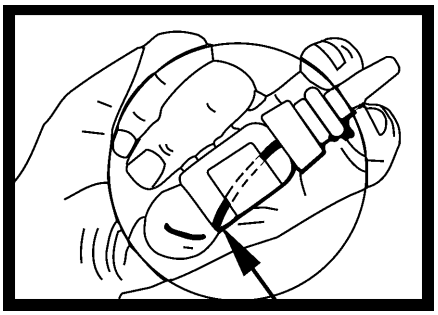
CAUTION: The nasal spray pump accurately delivers 50 doses of 10 micrograms each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter per actuation may be substantially less than 10 micrograms of drug. Do not transfer any remaining solution to another bottle. Please read the following instructions carefully before using the spray pump.

Using your DDAVP® Nasal Spray Pump

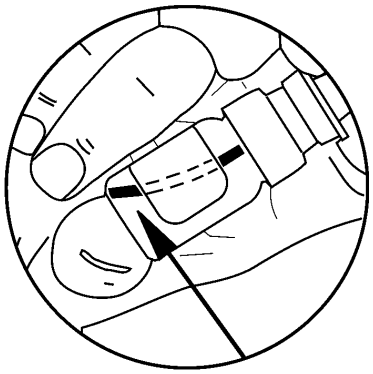
1. Remove protective cap.

2. **The spray pump must be primed prior to the first use.** To prime pump, press down 4 times.

3. Once primed, the spray pump delivers 10 micrograms of medication each time it is pressed. To ensure dosing accuracy, tilt bottle so that dip tube inside the bottle draws from the deepest portion of the medication.



CORRECT



INCORRECT

To administer a 10-microgram dose, place the spray nozzle in nostril and press the spray pump once. If a higher dose has been prescribed, spray half the dose in each nostril. The spray pump cannot be used for doses less than 10 micrograms or doses other than multiples of 10 micrograms.

4. Replace the protective cap on bottle after use. The pump will stay primed for up to one week. If the product has not been used for a period of one week, re-prime the pump by pressing once.

5. We have included a convenient check-off chart to assist you in keeping track of medication doses used. This will help assure that you receive 50 "full doses" of medication. Please note that the bottle has been filled with extra solution to accommodate the initial priming activity.

DDAVP® Nasal Spray
50-Dose Check-off

1	2	3	4	5
6	7	8	9	10
11	12	13	14	15
16	17	18	19	20
21	22	23	24	25
26	27	28	29	30
31	32	33	34	35
36	37	38	39	40
41	42	43	44	45
46	47	48	49	50

1. Retain with medication or affix in convenient location.

2. Starting with dose #1, check off after each administration.

3. **Discard medication after 50 doses.**

Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [see USP].

STORE BOTTLE IN UPRIGHT POSITION.

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