DDAVP®
Nasal Spray
(desmopressin acetate)

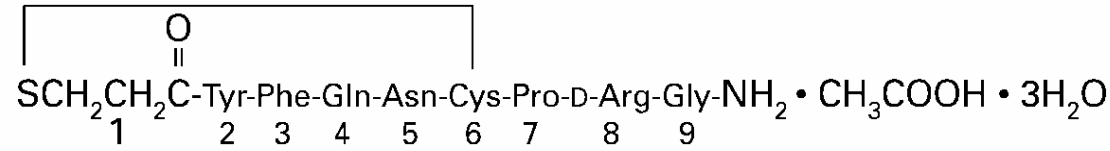
Rx only

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

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).

DDAVP is contraindicated in patients with hyponatremia or a history of hyponatremia.

WARNINGS

1. For intranasal use only.

2. **DDAVP Nasal Spray** should only be used in patients where orally administered formulations are not feasible.

3. Very rare cases of hyponatremia have been reported from world-wide postmarketing experience in patients treated with DDAVP (desmopressin acetate). DDAVP is a potent antidiuretic which, when administered, may lead to water intoxication and/or hyponatremia. Unless properly diagnosed and treated hyponatremia can be fatal. Therefore, fluid restriction is recommended and should be discussed with the patient and/or guardian. Careful medical supervision is required.

4. 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 (See **PRECAUTIONS**, Pediatric Use and Geriatric Use.) All patients receiving DDAVP therapy should be observed for the following signs or symptoms associated with hyponatremia: headache, nausea/vomiting, decreased serum sodium weight gain, restlessness, fatigue, lethargy, disorientation, depressed reflexes, loss of appetite, irritability, muscle weakness, muscle spasms or cramps and abnormal mental status such as hallucinations, decreased consciousness and confusion. Severe symptoms may include one or a combination of the following: seizure, coma and/or respiratory arrest. 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.

5. DDAVP should be used with caution in patients with habitual or psychogenic polydipsia who may be more likely to drink excessive amounts of water, putting them at greater risk of hyponatremia.

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, heart failure and renal disorders 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.

Information for Patients: Ensure that in children administration is under adult supervision in order to control the dose intake. 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.

Fluid intake should be adjusted downward based upon discussion with the physician.

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.

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. The concomitant administration of drugs that may increase the risk of water intoxication with hyponatremia, (e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine) should be performed with caution.

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: *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. (See **WARNINGS**.) 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
NERVOUS SYSTEM			
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Rhinitis	2	8	3
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

Post Marketing: There have been rare reports of hyponatremic convulsions associated with concomitant use with the following medications: oxybutinin and imipramine.

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

OVERDOSAGE

Signs of overdose may include confusion, drowsiness, continuing headache, problems with passing urine and rapid weight gain due to fluid retention. (See **WARNINGS**.) 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

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. Fluid restriction should be observed. (See **WARNINGS**, **PRECAUTIONS**, Pediatric Use and Geriatric Use.)

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 bottle, 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:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Rev. July 2007

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.

Ensure that in children administration is under adult supervision in order to control the dose intake.

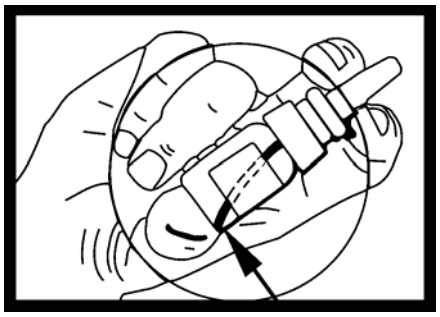
If you accidentally deliver/administer too much of a dose, immediately telephone your doctor or a certified Regional Poison Center for advice. Possible signs of overdose may include confusion, drowsiness, continuing headache, problems with passing urine and rapid weight gain due to fluid retention.

Using your DDAVP Nasal Spray Pump

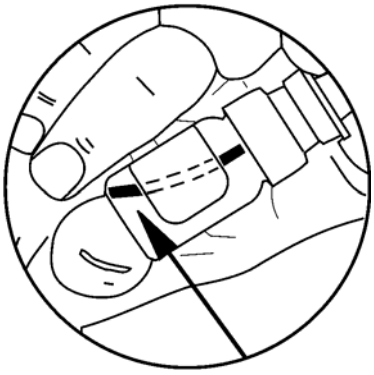
1. Remove protective cap.

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.

Manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Rev. July 2007

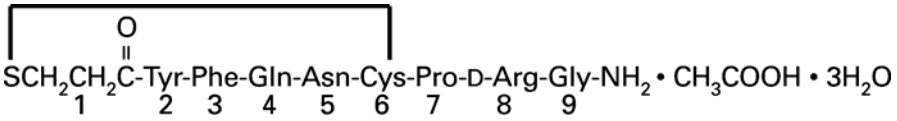
DDAVP®
Rhinal Tube
(desmopressin acetate)

Rx only

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 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

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 transsphenoidal 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**.

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

DDAVP is contraindicated in patients with hyponatremia or a history of hyponatremia.

WARNINGS

1. For intranasal use only.

2. **DDAVP Rhinal Tube** should only be used in patients where orally administered formulations are not feasible.

3. Very rare cases of hyponatremia have been reported from world-wide postmarketing experience in patients treated with DDAVP (desmopressin acetate). DDAVP is a potent antidiuretic which, when administered, may lead to water intoxication and/or hyponatremia. Unless properly diagnosed and treated hyponatremia can be fatal. Therefore, fluid restriction is recommended and should be discussed with the patient and/or guardian. Careful medical supervision is required.

4. 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 (See **PRECAUTIONS**, Pediatric Use and Geriatric Use.) All patients receiving DDAVP therapy should be observed for the following signs or symptoms associated with hyponatremia: headache, nausea/vomiting, decreased serum sodium weight gain, restlessness, fatigue, lethargy, disorientation, depressed reflexes, loss of appetite, irritability, muscle weakness, muscle spasms or cramps and abnormal mental status such as hallucinations, decreased consciousness and confusion. Severe symptoms may include one or a combination of the following: seizure, coma and/or respiratory arrest. 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.

5. DDAVP should be used with caution in patients with habitual or psychogenic polydipsia who may be more likely to drink excessive amounts of water, putting them at greater risk of hyponatremia.

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, heart failure and renal disorders because these patients are prone to hyponatremia.

Ensure that in children administration is under adult supervision in order to control the dose intake.

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.

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.

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. The concomitant administration of drugs that may increase the risk of water intoxication with hyponatremia, (e.g., tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine) should be performed with caution.

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. 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 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: *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. Fluid restriction should be discussed with the patient and/or guardian. (See **WARNINGS**.) 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.

Geriatric Use: Clinical studies of DDAVP Rhinal Tube 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 elderly and younger patients. 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 other 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 Rhinal Tube in geriatric patients will require careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed with the patient. (See **WARNINGS**.)

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 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
NERVOUS SYSTEM			
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Rhinitis	2	8	3
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

Post Marketing: There have been rare reports of hyponatremic convulsions associated with concomitant use with the following medications: oxybutinin and imipramine.

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

OVERDOSAGE

Signs of overdose may include confusion, drowsiness, continuing headache, problems with passing urine and rapid weight gain due to fluid retention. (See **WARNINGS.**) 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

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. Fluid restriction should be observed. (See **WARNINGS, PRECAUTIONS**, Pediatric Use and Geriatric Use.)

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 Rhinal Tube is available in a 2.5 mL bottle, 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 mcg (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).

Keep out of the reach of children.

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

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

Manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Rev. July 2007

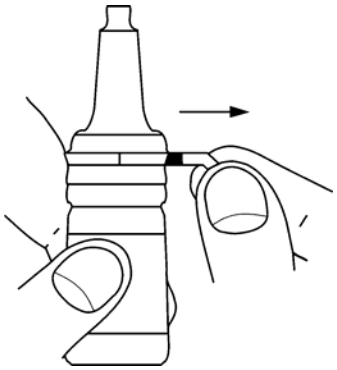
PATIENT INSTRUCTION GUIDE

DDAVP®
Rhinal Tube
(desmopressin acetate)

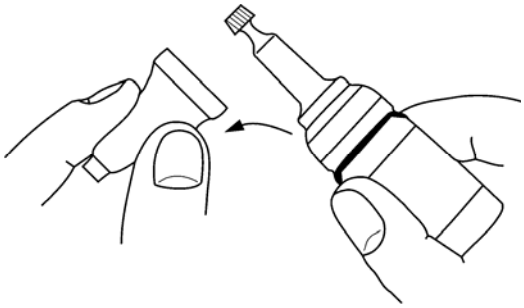
Ensure that in children administration is under adult supervision in order to control the dose intake.

If you accidentally deliver/administer too much of a dose, immediately telephone your doctor or a certified Regional Poison Center for advice. Possible signs of overdose may include confusion, drowsiness, continuing headache, problems with passing urine and rapid weight gain due to fluid retention.

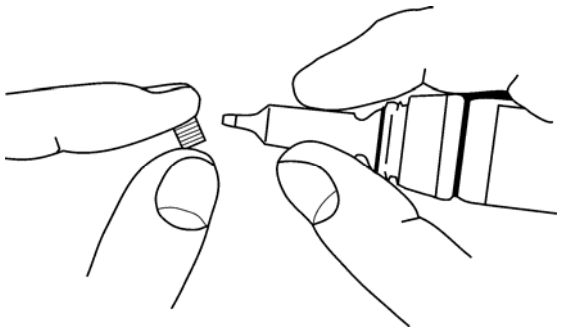
1. Pull plastic tag on neck of bottle.



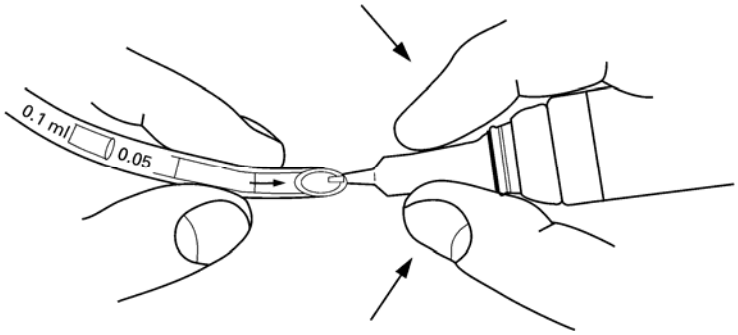
2. Break security seal and remove plastic cap.



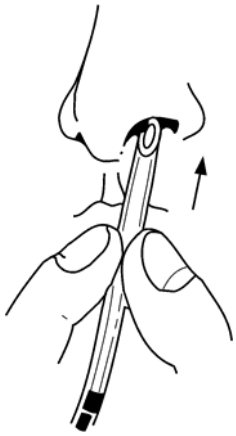
3. Twist off the small knurled seal from the dropper. **Use the same seal reversed to prevent subsequent leakage,** especially if the bottle is not stored upright.



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.

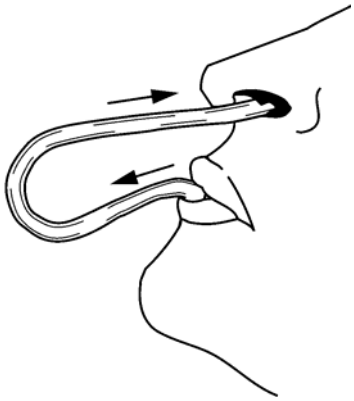


5. Hold the tube with the fingers approximately ¾ inch from the end and insert into a nostril until the tips of the fingers reach the nostril.



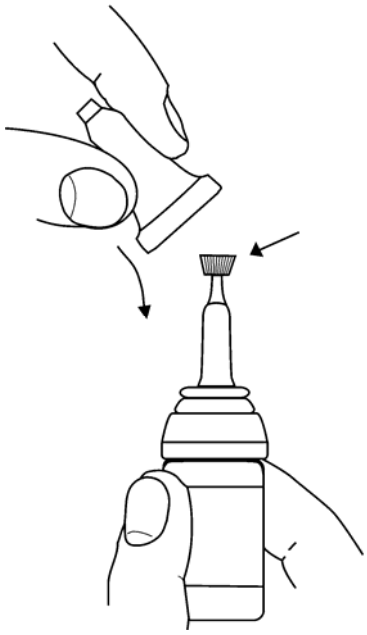
6. Put the other end of the tube into the mouth. Hold the breath, tilt the head back and then blow with a short, strong puff through the tube so that the solution reaches the right place in the nasal cavity. Through this procedure, medication is limited to the nasal cavity and the preparation does not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



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).

Manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Rev. July 2007

DDAVP® Injection

(desmopressin acetate)

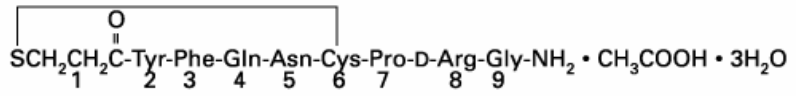
4 mcg/mL

Rx only

DESCRIPTION

DDAVP® Injection (desmopressin acetate) 4 mcg/mL 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 Injection 4 mcg/mL is provided as a sterile, aqueous solution for injection.

Each mL provides:

Desmopressin acetate	4.0 mcg
Sodium chloride	9.0 mg
Hydrochloric acid to adjust pH to 4	

The 10 mL vial contains chlorobutanol as a preservative (5.0 mg/mL).

CLINICAL PHARMACOLOGY

DDAVP Injection 4 mcg/mL contains as active substance, desmopressin acetate, a synthetic analogue of the natural hormone arginine vasopressin. One mL (4 mcg) of DDAVP (desmopressin acetate) solution has an antidiuretic activity of about 16 IU; 1 mcg of DDAVP is equivalent to 4 IU.

DDAVP has been shown to be more potent than arginine vasopressin in increasing plasma levels of factor VIII activity in patients with hemophilia and von Willebrand's disease Type I.

Dose-response studies were performed in healthy persons, using doses of 0.1 to 0.4 mcg/kg body weight, infused over a 10-minute period. Maximal dose response occurred at 0.3 to 0.4 mcg/kg. The response to DDAVP of factor VIII activity and plasminogen activator is dose-related, with maximal plasma levels of 300 to 400 percent of initial concentrations obtained after infusion of 0.4 mcg/kg body weight. The increase is rapid and evident within 30 minutes, reaching a maximum at a point ranging from 90 minutes to two hours. The factor VIII related antigen and ristocetin cofactor activity were also increased to a smaller degree, but still are dose-dependent.

1. The biphasic half-lives of DDAVP were 7.8 and 75.5 minutes for the fast and slow phases, respectively, compared with 2.5 and 14.5 minutes for lysine vasopressin, another form of the hormone. As a result, 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. When administered by injection, DDAVP has an antidiuretic effect about ten times that of an equivalent dose administered intranasally.
4. The bioavailability of the subcutaneous route of administration was determined qualitatively using urine output data. The exact fraction of drug absorbed by that route of administration has not been quantitatively determined.
5. The percentage increase of factor VIII levels in patients with mild hemophilia A and von Willebrand's disease was not significantly different from that observed in normal healthy individuals when treated with 0.3 mcg/kg of DDAVP infused over 10 minutes.
6. Plasminogen activator activity increases rapidly after DDAVP infusion, but there has been no clinically significant fibrinolysis in patients treated with DDAVP.
7. The effect of repeated DDAVP administration when doses were given every 12 to 24 hours has generally shown a gradual diminution of the factor VIII activity increase noted with a single dose. The initial response is reproducible in any particular patient if there are 2 or 3 days between administrations.

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

Hemophilia A: DDAVP Injection 4 mcg/mL is indicated for patients with hemophilia A with factor VIII coagulant activity levels greater than 5%.

DDAVP will often maintain hemostasis in patients with hemophilia A during surgical procedures and postoperatively when administered 30 minutes prior to scheduled procedure.

DDAVP will also stop bleeding in hemophilia A patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding.

DDAVP is not indicated for the treatment of hemophilia A with factor VIII coagulant activity levels equal to or less than 5%, or for the treatment of hemophilia B, or in patients who have factor VIII antibodies.

In certain clinical situations, it may be justified to try DDAVP in patients with factor VIII levels between 2% to 5%; however, these patients should be carefully monitored.

von Willebrand's Disease (Type I): DDAVP Injection 4 mcg/mL is indicated for patients with mild to moderate classic von Willebrand's disease (Type I) with factor VIII levels greater than 5%. DDAVP will often maintain hemostasis in patients with mild to moderate von Willebrand's disease during surgical procedures and postoperatively when administered 30 minutes prior to the scheduled procedure.

DDAVP will usually stop bleeding in mild to moderate von Willebrand's patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding.

Those von Willebrand's disease patients who are least likely to respond are those with severe homozygous von Willebrand's disease with factor VIII coagulant activity and factor VIII von Willebrand factor antigen levels less than 1%. Other patients may respond in a variable fashion depending on the type of molecular defect they have. Bleeding time and factor VIII coagulant activity, ristocetin cofactor activity, and von Willebrand factor antigen should be checked during administration of DDAVP to ensure that adequate levels are being achieved.

DDAVP is not indicated for the treatment of severe classic von Willebrand's disease (Type I) and when there is evidence of an abnormal molecular form of factor VIII antigen. (See **WARNINGS.**)

Diabetes Insipidus: DDAVP Injection 4 mcg/mL is indicated as antidiuretic replacement therapy in the management of central (cranial) diabetes insipidus and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. DDAVP is ineffective for the treatment of nephrogenic diabetes insipidus.

DDAVP is also available as an intranasal preparation. However, this means of delivery can be compromised by a variety of factors that can make nasal insufflation ineffective or inappropriate. These include poor intranasal absorption, nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. Intranasal delivery may 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 Injection 4 mcg/mL is contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of **DDAVP Injection** 4 mcg/mL**.**

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

DDAVP is contraindicated in patients with hyponatremia or a history of hyponatremia.

WARNINGS

1. Very rare cases of hyponatremia have been reported from world-wide postmarketing experience in patients treated with DDAVP (desmopressin acetate). DDAVP is a potent antidiuretic which, when administered, may lead to water intoxication and/or hyponatremia. Unless properly diagnosed and treated hyponatremia can be fatal. Therefore, fluid restriction is recommended and should be discussed with the patient and/or guardian. Careful medical supervision is required.

2. When DDAVP Injection is administered to patients who do not have need of antidiuretic hormone for its antidiuretic effect, in particular in pediatric and geriatric patients, fluid intake should be adjusted downward to decrease the potential occurrence of water intoxication and hyponatremia. (See **PRECAUTIONS**, Pediatric Use and Geriatric Use.) All patients receiving DDAVP therapy should be observed for the following signs of symptoms associated with hyponatremia: headache, nausea/vomiting, decreased serum sodium, weight gain, restlessness, fatigue, lethargy, disorientation, depressed reflexes, loss of appetite, irritability, muscle weakness, muscle spasms or cramps and abnormal mental status such as hallucinations, decreased consciousness and confusion. Severe symptoms may include one or a combination of the following: seizure, coma and/or respiratory arrest. 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.

3. DDAVP should not be used to treat patients with Type IIB von Willebrand's disease since platelet aggregation may be induced.

4. DDAVP should be used with caution in patients with habitual or psychogenic polydipsia who may be more likely to drink excessive amounts of water, putting them at greater risk of hyponatremia.

PRECAUTIONS

General: For injection use only.

DDAVP Injection (desmopressin acetate) 4 mcg/mL has infrequently produced changes in blood pressure causing either a slight elevation in blood pressure or a transient fall in blood pressure and a compensatory increase in heart rate. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease.

DDAVP (desmopressin acetate) should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, heart failure and renal disorders, because these patients are prone to hyponatremia.

There have been rare reports of thrombotic events following **DDAVP Injection** 4 mcg/mL in patients predisposed to thrombus formation. No causality has been determined, however, the drug should be used with caution in these patients.

Severe allergic reactions have been reported rarely. Anaphylaxis has been reported rarely with intravenous and intranasal DDAVP, including isolated cases of fatal anaphylaxis with intravenous DDAVP. It is not known whether antibodies to **DDAVP Injection** 4 mcg/mL are produced after repeated injections.

Hemophilia A: Laboratory tests for assessing patient status include levels of factor VIII coagulant, factor VIII antigen and factor VIII ristocetin cofactor (von Willebrand factor) as well as activated partial thromboplastin time. Factor VIII coagulant activity should be determined before giving DDAVP for hemostasis. If factor VIII coagulant activity is present at less than 5% of normal, DDAVP should not be relied on.

von Willebrand's Disease: Laboratory tests for assessing patient status include levels of factor VIII coagulant activity, factor VIII ristocetin cofactor activity, and factor VIII von Willebrand factor antigen. The skin bleeding time may be helpful in following these patients.

Diabetes Insipidus: Laboratory tests for monitoring the patient include urine volume and osmolality. In some cases, plasma osmolality may be required.

Drug Interactions: Although the pressor activity of DDAVP is very low compared with the antidiuretic activity, use of doses as large as 0.3 mcg/kg of DDAVP with other pressor agents should be done only with careful patient monitoring. The concomitant administration of drugs that may increase the risk of water intoxication with hyponatremia, (e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine) should be performed with caution.

DDAVP has been used with epsilon aminocaproic acid without adverse effects.

Carcinogenicity, Mutagenicity, 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. 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 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: Use in infants and pediatric patients will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed with the patient and/or guardian. (See **WARNINGS**.) **DDAVP Injection** 4 mcg/mL *should not be used in infants less than three months of age* in the treatment of hemophilia A or von Willebrand's disease; safety and effectiveness in pediatric patients under 12 years of age with diabetes insipidus have not been established.

Geriatric Use: Clinical studies of DDAVP Injection 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 patients. In general, dose selection 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 other 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 injection in geriatric patients will require careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed with the patient. (See **WARNINGS**.)

ADVERSE REACTIONS

Infrequently, DDAVP has produced transient headache, nausea, mild abdominal cramps and vulval pain. These symptoms disappeared with reduction in dosage. Occasionally, injection of DDAVP has produced local erythema, swelling or burning pain. Occasional facial flushing has been reported with the administration of DDAVP. **DDAVP Injection** has infrequently produced changes in blood pressure causing either a slight elevation or a transient fall and a compensatory increase in heart rate. Severe allergic reactions including anaphylaxis have been reported rarely with **DDAVP Injection**.

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

Post Marketing: There have been rare reports of thrombotic events (acute cerebrovascular thrombosis, acute myocardial infarction) following **DDAVP Injection** in patients predisposed to thrombus formation, and rare reports of hyponatremic convulsions associated with concomitant use with the following medications: oxybutinin and imipramine.

OVERDOSAGE

Signs of overdose may include confusion, drowsiness, continuing headache, problems with passing urine and rapid weight gain due to fluid retention. (See **WARNINGS**.) In case of overdosage, the dosage 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 Injection** 4 mcg/mL.

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

DOSAGE AND ADMINISTRATION

Hemophilia A and von Willebrand's Disease (Type I): DDAVP Injection 4 mcg/mL is administered as an intravenous infusion at a dose of 0.3 mcg DDAVP/kg body weight diluted in sterile physiological saline and infused slowly over 15 to 30 minutes. In adults and children weighing more than 10 kg, 50 mL of diluent is recommended; in children weighing 10 kg or less, 10 mL of diluent is recommended. Blood pressure and pulse should be monitored during infusion. If **DDAVP Injection** 4 mcg/mL is used preoperatively, it should be administered 30 minutes prior to the scheduled procedure.

The necessity for repeat administration of DDAVP or use of any blood products for hemostasis should be determined by laboratory response as well as the clinical condition of the patient. The tendency toward tachyphylaxis (lessening of response) with repeated administration given more frequently than every 48 hours should be considered in treating each patient.

Fluid restriction should be observed. (See **WARNINGS, PRECAUTIONS**, Pediatric Use and Geriatric Use.)

Diabetes Insipidus: This formulation is administered subcutaneously or by direct intravenous injection. **DDAVP Injection** 4 mcg/mL dosage must be determined for each patient and adjusted according to the pattern of response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water turnover.

The usual dosage range in adults is 0.5 mL (2.0 mcg) to 1 mL (4.0 mcg) daily, administered intravenously or subcutaneously, usually in two divided doses. The morning and evening doses should be separately adjusted for an adequate diurnal rhythm of water turnover. For patients who have been controlled on intranasal DDAVP and who must be switched to the injection form, either because of poor intranasal absorption or because of the need for surgery, the comparable antidiuretic dose of the injection is about one-tenth the intranasal dose.

Fluid restriction should be observed. (See **WARNINGS, PRECAUTIONS**, Pediatric Use and Geriatric Use.)

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

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.)

Directions for use of One Point Cut (OPC) Ampules for DDAVP Injection:

1. Use aseptic technique to clean ampule. Gently tap the top of the ampule to assist the flow of the solution from the upper portion of the ampule to the lower portion.
2. Locate the blue dot on the upper portion of the ampule. **Below** this dot is a small score on the neck of the ampule. Hold the ampule with the blue dot **facing away from you**.
3. Cover the vial with an appropriate wipe. Apply pressure to the top and bottom portions of the ampule to snap the ampule open away from you.

HOW SUPPLIED

DDAVP Injection 4 mcg/mL is available as a sterile solution in cartons of ten 1 mL single-dose ampules (NDC 0075-2451-01) and in 10 mL multiple-dose vials (NDC 0075-2451-53), each containing 4.0 mcg DDAVP per mL.

Store refrigerated 2 to 8°C (36 to 46°F).

Keep out of the reach of children.

Manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

1.1 US Patents 5,500,413; 5,596,078; 5,763,407

Rev. July 2007

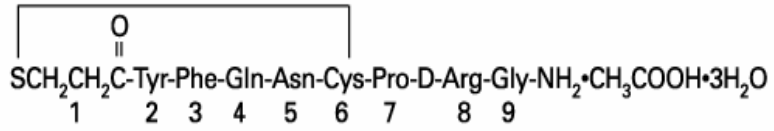
DDAVP® Tablets
(desmopressin acetate)

Rx only

DESCRIPTION

DDAVP® Tablets (desmopressin acetate) are 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 Tablets contain either 0.1 or 0.2 mg desmopressin acetate. Inactive ingredients include: lactose, potato starch, magnesium stearate and povidone.

CLINICAL PHARMACOLOGY

DDAVP Tablets contain as active substance, desmopressin acetate, a synthetic analogue of the natural hormone arginine vasopressin.

Central Diabetes Insipidus: Dose response studies in patients with diabetes insipidus have demonstrated that oral doses of 0.025 mg to 0.4 mg produced clinically significant antidiuretic effects. In most patients, doses of 0.1 mg to 0.2 mg produced optimal antidiuretic effects lasting up to eight hours. With doses of 0.4 mg, antidiuretic effects were observed for up to 12 hours; measurements beyond 12 hours were not recorded. Increasing oral doses produced dose dependent increases in the plasma levels of DDAVP (desmopressin acetate).

The plasma half-life of DDAVP followed a monoexponential time course with $t_{1/2}$ values of 1.5 to 2.5 hours which was independent of dose.

The bioavailability of DDAVP oral tablets is about 5% compared to intranasal DDAVP, and about 0.16% compared to intravenous DDAVP. The time to reach maximum plasma DDAVP levels ranged from 0.9 to 1.5 hours following oral or intranasal administration, respectively. Following administration of **DDAVP Tablets**, the onset of antidiuretic effect occurs at around 1 hour, and it reaches a maximum at about 4 to 7 hours based on the measurement of increased urine osmolality.

The use of **DDAVP Tablets** in patients with an established diagnosis will result in a reduction in urinary output with an accompanying increase in urine osmolality. These effects usually will allow resumption of a more normal life style, with a decrease in urinary frequency and nocturia.

There are reports of an occasional change in response to the intranasal formulations of DDAVP (DDAVP Nasal Spray and DDAVP Rhinal Tube). Usually, the change occurred over a period of time greater than six months. This change may be due to decreased responsiveness, or to shortened duration of effect. There is no evidence that this effect is due to the development of binding antibodies, but may be due to a local inactivation of the peptide. No lessening of effect was observed in the 46 patients who were treated with **DDAVP Tablets** for 12 to 44 months and no serum antibodies to desmopressin were detected.

The change in structure of arginine vasopressin to desmopressin acetate resulted in less vasopressor activity and decreased action on visceral smooth muscle relative to enhanced antidiuretic activity. Consequently, clinically effective antidiuretic doses are usually below the threshold for effects on vascular or visceral smooth muscle. In the four long-term studies of **DDAVP Tablets**, no increases in blood pressure in 46 patients receiving **DDAVP Tablets** for periods of 12 to 44 months were reported.

In one study, the pharmacodynamic characteristics of **DDAVP Tablets** and intranasal formulation were compared during an 8-hour dosing interval at steady state. The doses administered to 36 hydrated (water loaded) healthy male adult volunteers every 8 hours were 0.1, 0.2, 0.4 mg orally and 0.01 mg intranasally by rhinal tube. The results are shown in the following table:

Mean Changes from Baseline (SE) in Pharmacodynamic Parameters in Normal Healthy Adult Volunteers

Treatment	Total Urine Volume in mL	Maximum Urine Osmolality in mOsm/kg
0.1 mg PO q8h	-3689.3 (149.6)	514.8 (21.9)
0.2 mg PO q8h	-4429.9 (149.6)	686.3 (21.9)
0.4 mg PO q8h	-4998.8 (149.6)	769.3 (21.9)
0.01 mg IN q8h	-4844.9 (149.6)	754.1 (21.9)

(SE) = Standard error of the mean

With respect to the mean values of total urine volume decrease and maximum urine osmolality increase from baseline, the 90% confidence limits estimated that the 0.4 mg and 0.2 mg oral dose produced between 95% and 110% and 84% to 99% of pharmacodynamic activity, respectively, when compared to the 0.01 mg intranasal dose.

While both the 0.2 mg and 0.4 mg oral doses are considered pharmacodynamically similar to the 0.01 mg intranasal dose, the pharmacodynamic data on an inter-subject basis was highly variable and, therefore, individual dosing is recommended.

In another study in diabetes insipidus patients, the pharmacodynamic characteristics of **DDAVP Tablets** and intranasal formulations were compared over a 12-hour period. Ten fluid-controlled patients under age 18 were administered tablet doses of 0.2 mg and 0.4 mg, and intranasal doses of 0.01 mg and 0.02 mg.

Mean Peak Pharmacodynamic Parameters (SD) in Pediatric and Adolescent Diabetes Insipidus Patients

Treatment	Urine Volume in mL/min	Maximum Urine Osmolality in mOsm/kg
0.01 mg IN	0.3 (0.15)	717.0 (224.63)
0.02 mg IN	0.3 (0.25)	761.8 (298.82)
0.2 mg PO	0.3 (0.12)	678.3 (147.91)
0.4 mg PO	0.2 (0.15)	787.2 (73.34)

(SD) = Standard Deviation

All four dose formulations (0.01 mg IN, 0.02 mg IN, 0.2 mg PO and 0.4 mg PO) have a similar, pronounced pharmacodynamic effect on urine volume and urine osmolality. At two hours after study drug administration, mean urine volume was 4 mL/min and urine osmolality was >500 mOsm/kg. Mean plasma osmolality remained relatively constant over the time course recorded (0 to 12 hours). A statistical separation from baseline did not occur at any dose or time point. In these patients, the 0.2 mg tablets and the 0.01 mg intranasal spray exhibited similar pharmacodynamic profiles as did the 0.4 mg tablets and the 0.02 mg intranasal spray formulation. In another study of adult diabetes insipidus patients previously controlled on

DDAVP intranasal spray, after one week of self-titration from spray to tablets, patients' diuresis was controlled with 0.1 mg **DDAVP Tablets** three times a day.

Primary Nocturnal Enuresis: Two double-blind, randomized, placebo-controlled studies were conducted in 340 patients with primary nocturnal enuresis. Patients were 5-17 years old, and 72% were males. A total of 329 patients were evaluated for efficacy. Patients were evaluated over a two-week baseline period in which the average number of wet nights was 10 (range 4-14). Patients were then randomized to receive 0.2, 0.4, or 0.6 mg of DDAVP or placebo. The pooled results after two weeks are shown in the following table:

Response to DDAVP and Placebo at Two Weeks of Treatment
Mean (SE) Number of Wet Nights/2 Weeks

	Placebo (n = 85)	**0.2 mg/day (n = 79)**	**0.4 mg/day (n = 82)**	**0.6 mg/day (n = 83)**
Baseline	10 (0.3)	11 (0.3)	10 (0.3)	10 (0.3)
Reduction from Baseline	1 (0.3)	3 (0.4)	3 (0.4)	4 (0.4)
Percent Reduction from Baseline	10%	27%	30%	40%
p-value vs placebo	----	<0.05	<0.05	<0.05

Patients treated with **DDAVP Tablets** showed a statistically significant reduction in the number of wet nights compared to placebo-treated patients. A greater response was observed with increasing doses up to 0.6 mg.

In a six month, open-label extension study, patients completing the placebo-controlled studies were started on 0.2 mg/day DDAVP, and the dose was progressively increased until the optimal response was achieved (maximum dose 0.6 mg/day). A total of 230 patients were evaluated for efficacy; the average number of wet nights/2 weeks during the untreated baseline period was 10 (range 4-14), and the average duration (SD) of treatment was 4.2 (1.8) months. Twenty-five (25) patients (11%) achieved a complete or near complete response (≤2 wet nights/2 weeks) and did not require titration to the 0.6 mg/day dose. The majority of patients (198 of 230, 86%) were titrated to the highest dose. When all dose groups were combined, 128 (56%) showed at least a 50% reduction from baseline in the number of wet nights/2 weeks, while 87 (38%) patients achieved a complete or near complete response.

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

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

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

Primary Nocturnal Enuresis: DDAVP Tablets are indicated for the management of primary nocturnal enuresis. DDAVP may be used alone or as an adjunct to behavioral conditioning or other non-pharmacologic intervention.

CONTRAINDICATIONS

DDAVP Tablets are contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of **DDAVP Tablets**.

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

DDAVP is contraindicated in patients with hyponatremia or a history of hyponatremia.

WARNINGS

1. Very rare cases of hyponatremia have been reported from world-wide postmarketing experience in patients treated with DDAVP (desmopressin acetate). DDAVP is a potent antidiuretic which, when administered, may lead to water intoxication and/or hyponatremia. Unless properly diagnosed and treated hyponatremia can be fatal. Therefore, fluid restriction is recommended and should be discussed with the patient and/or guardian. Careful medical supervision is required.

2. When DDAVP Tablets are administered, in particular in pediatric and geriatric patients, fluid intake should be adjusted downward to decrease the potential occurrence of water intoxication and hyponatremia. (See **PRECAUTIONS**, Pediatric Use and Geriatric Use.) All patients receiving DDAVP therapy should be observed for the following signs of symptoms associated with hyponatremia: headache, nausea/vomiting, decreased serum sodium, weight gain, restlessness, fatigue, lethargy, disorientation, depressed reflexes, loss of appetite, irritability, muscle weakness, muscle spasms or cramps and abnormal mental status such as hallucinations, decreased consciousness and confusion. Severe symptoms may include one or a combination of the following: seizure, coma and/or respiratory arrest. 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.

3. DDAVP should be used with caution in patients with habitual or psychogenic polydipsia who may be more likely to drink excessive amounts of water, putting them at greater risk of hyponatremia.

PRECAUTIONS

General: Intranasal formulations of DDAVP at high doses and DDAVP Injection have infrequently produced a slight elevation of blood pressure which disappears with a reduction of dosage. Although this effect has not been observed when single oral doses up to 0.6 mg have been administered, the drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease, because of a 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, heart failure and renal disorders 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 but not with **DDAVP Tablets**.

Laboratory Tests: *Central Diabetes Insipidus:* Laboratory tests for monitoring the patient with central diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases, measurements of plasma osmolality may be useful.

Drug Interactions: Although the pressor activity of DDAVP is very low compared to its antidiuretic activity, large doses of **DDAVP Tablets** should be used with other pressor agents only with careful patient monitoring. The concomitant administration of drugs that may increase the risk of water intoxication with hyponatremia, (e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine) should be performed with caution.

Carcinogenicity, Mutagenicity, 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 studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Several publications where desmopressin acetate was used 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 possible 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 in breast milk following an intranasal dose of 0.01 mg.

It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DDAVP is administered to nursing mothers.

Pediatric Use: *Central Diabetes Insipidus:* **DDAVP Tablets** (desmopressin acetate) have been used safely in pediatric patients, age 4 years and older, with diabetes insipidus for periods up to 44 months. In younger pediatric patients the dose must be individually adjusted in order to prevent an excessive decrease in plasma osmolality leading to hyponatremia and possible convulsions; dosing should start at 0.05 mg (1/2 of the 0.1 mg tablet). Use of **DDAVP Tablets** in pediatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed with the patient and/or guardian. (See **WARNINGS**.)

Primary Nocturnal Enuresis: **DDAVP Tablets** have been safely used in pediatric patients age 6 years and older with primary nocturnal enuresis for up to 6 months. Some patients respond to a dose of 0.2 mg; however, increasing responses are seen at doses of 0.4 mg and 0.6 mg. No increase in the frequency or severity of adverse reactions or decrease in efficacy was seen with an increased dose or duration. The dose should be individually adjusted to achieve the best results. Treatment with desmopressin for primary nocturnal enuresis should be interrupted during acute intercurrent illness characterized by fluid and/or electrolyte imbalance (e.g., systemic infections, fever, recurrent vomiting or diarrhea) or under conditions of extremely hot weather, vigorous exercise or other conditions associated with increased water intake.

Geriatric Use: Clinical studies of DDAVP Tablets 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 patients. 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 other 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 Tablets in geriatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed with the patient. (See **WARNINGS**.)

ADVERSE REACTIONS

Infrequently, large doses of the intranasal formulations of DDAVP and DDAVP Injection have produced transient headache, nausea, flushing and mild abdominal cramps. These symptoms have disappeared with reduction in dosage.

Central Diabetes Insipidus: In long-term clinical studies in which patients with diabetes insipidus were followed for periods up to 44 months of **DDAVP Tablet** therapy, transient increases in AST (SGOT) no higher than 1.5 times the upper limit of normal were occasionally observed. Elevated AST (SGOT) returned to the normal range despite continued use of **DDAVP Tablets**.

Primary Nocturnal Enuresis: The only adverse event occurring in ≥3% of patients in controlled clinical trials with **DDAVP Tablets** that was probably, possibly, or remotely related to study drug was headache (4% DDAVP, 3% placebo).

Other: The following adverse events have been reported; however their relationship to DDAVP has not been established: abnormal thinking, diarrhea, and edema-weight gain.

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

Post Marketing: There have been rare reports of hyponatremic convulsions associated with concomitant use with the following medications: oxybutinin and imipramine.

OVERDOSAGE

Signs of overdose may include confusion, drowsiness, continuing headache, problems with passing urine and rapid weight gain due to fluid retention. (See **WARNINGS**.) In case of overdose, 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 DDAVP. The patient should be observed and treated with appropriate symptomatic therapy.

An oral LD_{50} has not been established. Oral doses up to 0.2 mg/kg/day have been administered to dogs and rats for 6 months without any significant drug-related toxicities reported. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

DOSAGE AND ADMINISTRATION

Central Diabetes Insipidus: The dosage of **DDAVP Tablets** 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 previously on intranasal DDAVP therapy should begin tablet therapy twelve hours after the last intranasal dose. During the initial dose titration period, patients should be

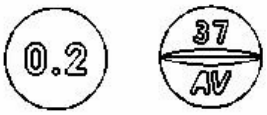
observed closely and appropriate safety parameters measured to assure adequate response. Patients should be monitored at regular intervals during the course of **DDAVP Tablet** therapy to assure adequate antidiuretic response. Modifications in dosage regimen should be implemented as necessary to assure adequate water turnover. Fluid restriction should be observed. (See **WARNINGS, PRECAUTIONS**, Pediatric Use and Geriatric Use.)

Adults and Children: 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. Most patients in clinical trials found that the optimal dosage range is 0.1 mg to 0.8 mg daily, administered in divided doses. Each dose should be separately adjusted for an adequate diurnal rhythm of water turnover. 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. See **Pediatric Use** subsection for special considerations when administering desmopressin acetate to pediatric diabetes insipidus patients.

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.)

Primary Nocturnal Enuresis: The dosage of **DDAVP Tablets** must be determined for each individual patient and adjusted according to response. Patients previously on intranasal DDAVP therapy can begin tablet therapy the night following (24 hours after) the last intranasal dose. The recommended initial dose for patients age 6 years and older is 0.2 mg at bedtime. The dose may be titrated up to 0.6 mg to achieve the desired response. Fluid restriction should be observed, and fluid intake should be limited to a minimum from 1 hour before desmopressin administration, until the next morning, or at least 8 hours after administration. (See **WARNINGS, PRECAUTIONS**, Pediatric Use and Geriatric Use.)

HOW SUPPLIED

Strength	**Size**	**NDC 0075-**	**Color**	**Markings**
0.1 mg	Bottle of 100	0016-00	White	
0.2 mg	Bottle of 100	0026-00	White	

Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [see USP]. Avoid exposure to excessive heat or light.

This product should be dispensed in a container with a child-resistant cap.

Keep out of the reach of children.

U.S. Patent Nos. 5,500,413; 5,596,078; 5,674,850; 5,047,398; 5,763,407

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