PACKAGE INSERT

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

DDAVP® Intranasal Solution 0,1 mg/ml - Multidose

COMPOSITION:

Each ml contains 0,1 mg desmopressin acetate equivalent to 0,089 mg **DDAVP®** (desmopressin) in an isotonic solution to pH 4.

The solution contains chlorobutanol 0,5 % m/v as preservative.

PHARMACOLOGICAL CLASSIFICATION:

A 18.2 Genito-urinary system – Antidiuretics.

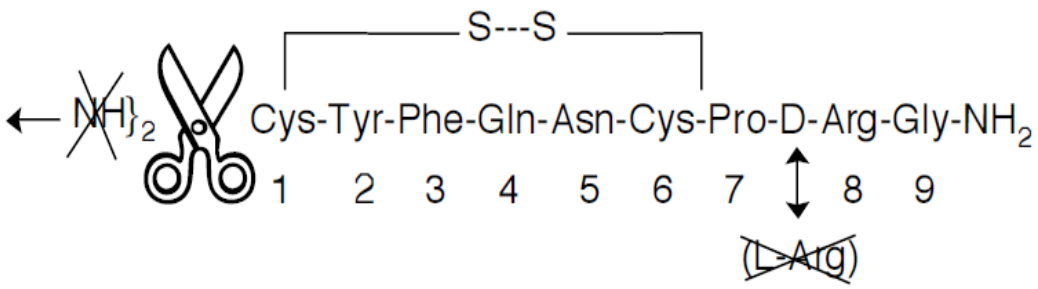
PHARMACOLOGICAL ACTION:

DDAVP® (desmopressin) is a synthetic structural analogue of the natural human hormone, arginine vasopressin (AVP).

The molecule has undergone two changes:

1. At the N-terminal position 1 the amino group has been removed.

2. L-arginine in position 8 has been replaced by D-arginine.



The clinical significance of this changed ratio of antidiuretic to vasopressor effect is that clinically active antidiuretic doses are far below the threshold level for a vasopressor effect, with a consequent reduction in unwanted pressor side effects.

Moreover, the change in the molecule has also resulted in a considerable increase in the otherwise very short half-life for vasopressin. Frequency of dosage is thus greatly reduced. **DDAVP®** (desmopressin) has considerable advantage over natural or synthetic lysine-vasopressin (LVP).

INDICATIONS

a) Diagnosis of central diabetes insipidus:

   Adult patients should be given a 1 litre oral water load initially and urine flow rate stabilised by giving oral fluids equivalent in volume to the volume of urine passed. The 20 µg **DDAVP®** is administered intranasally. This will be followed by a sharp decrease in urine flow rate and an increase in urine osmolality within 2 hours if the patient has vasopressin sensitive diabetes insipidus.

b) **DDAVP®** is indicated for the treatment of vasopressin sensitive central diabetes insipidus or in the treatment of post hypophysectomy polyuria and polydipsia.

c) Renal function testing:

Adults and children with normal renal function can be expected to achieve concentrations above 800 mOsm/kg in the period of 5 - 9 hours following intranasal administration of 40 µg and 20 µg **DDAVP®**, respectively.

It is recommended that the bladder should be emptied at the time of **DDAVP®** administration. A restricted water intake must be observed (see **Warnings**). In infants normal urine concentration of 600 mOsm/kg should be achieved in the 5-hour period following administration. Infants should be given a 10 µg intranasal dose of **DDAVP®** and the fluid intake at the two meals after administration restricted to 50 % of the ordinary intake in order to avoid water overload.

d) **DDAVP®** is indicated for the symptomatic short term (4 - 8 weeks) treatment of primary nocturnal enuresis in both young and adult patients (children older than 5 years) who have normal ability to concentrate urine. Safety in the elderly has not been established.

CONTRAINDICATIONS

DDAVP® must not be used in cases of:

1. Renal diabetes insipidus.
2. Hypersensitivity to **DDAVP®**.
3. Peripheral vascular disease.
4. History of known or suspected cardiac insufficiency and other conditions requiring treatment with diuretic agents.
5. Hypersensitivity to the preservative.
6. Habitual and psychogenic polydipsia
7. Cirrhosis.
8. Hypertension.
9. Cerebral vascular disease.

10. Moderate or severe renal insufficiency (creatinine clearance below 50 ml/min).
11. Known hyponatraemia.
12. Syndrome of inappropriate ADH secretion (SIADH).

WARNINGS

Overhydration:

The risk of overhydration including cardiac failure should be borne in mind, especially in children or the elderly and when **DDAVP®** is being used to test renal concentrating capacity or the patient is on fluid supplements either orally or parenterally.

Children should be closely observed to avoid over-ingestion of fluid. Excessive water intake can produce hyponatraemia with associated effects, including convulsions.

DDAVP® intranasal solution should be used with caution in:

- the very young and elderly patients.
- conditions characterised by fluid and/or electrolyte imbalance.
- patients at risk for increased intracranial pressure.

DDAVP® intranasal solution should only be used in patients where orally administered formulations are not feasible.

When **DDAVP®** intranasal solution is prescribed it is recommended

- To start at the lowest dose.
- To ensure compliance with fluid restriction instructions.
- To increase dose progressively, with caution.
- To ensure that in children administration is under adult supervision in order to control the dose intake.

In case of treatment of enuresis the fluid intake must be limited to a minimum and only to satisfy thirst from 1 hour before until 8 hours after administration.

Renal concentration capacity testing in children below the age of 1 year should only be performed in hospital and under careful supervision.
When used for diagnostic purposes the fluid intake must be limited and not exceed 0,5 litre from 1 hour before until 8 hours after administration.

INTERACTIONS

Substances which are known to release antidiuretic hormone, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine, may cause an additive antidiuretic effect and increase the risk of water retention and dilutional hyponatraemia. This may lead to convulsions.

NSAIDs may induce fluid retention/hyponatraemia (see **Side effects and special precautions**)

Indomethacin in combination with **DDAVP®** increases the magnitude but not the duration, of the response to **DDAVP®**.

Glibenclamide: A few cases, where the antidiuretic response induced by **DDAVP®** was reduced, were reported.

Carbamazepine may also prolong the action of **DDAVP®**.

Pressor agents – Large doses of **DDAVP®** together with other pressor agents should only be given with careful monitoring.

PREGNANCY AND LACTATION

Pregnancy:

Safety in pregnancy and lactation has not been established.

Lactation:

Results from analysis of milk from nursing mothers receiving a high dose of desmopressin (300 µg intranasally), indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.

DOSAGE AND DIRECTIONS FOR USE

Indications:

a) Diagnosis of central diabetes insipidus.
b) Vasopressin sensitive central diabetes insipidus, post hypophysectomy polyuria and polydipsia.
c) Renal function testing (see note below).
d) Nocturnal enuresis (see separate dosage instructions).

To institute therapy with **DDAVP®**, patients should be withdrawn from previous medication and allowed to establish a baseline polyuria and polydipsia. The stable polyuria is used as a baseline to determine the magnitude and duration of the response to medication. In less severe cases, prior water loading may be desirable to establish a vigorous flow of urine. When the urine osmolality reaches a plateau at the low level (in most cases, less than 100 mOsm per

kilogram), the first dose of **DDAVP®** is administered intranasally.

A urine sample is obtained after two hours and hourly thereafter following **DDAVP®** administration. Samples are measured for volume and osmolality. When the patient has reached the previous baseline urine osmolality and urine flow the medication effect has ceased and the next dose of **DDAVP®** is administered. The cycle is then repeated until the patient has reached a stable condition.

DDAVP® is dosed individually after testing the effect of different doses on urine osmolality and diuresis (according to the procedure described in the above paragraph). A summary of the therapeutic results in patients who have hitherto been treated with **DDAVP®** makes the following suggestion of an average dosage possible.

Central diabetes insipidus:

Children: 0,05 - 0,1 ml (5 – 10 µg) 1 – 2 times daily, intranasally.

Adults: 0,1 - 0,2 ml (10 - 20 µg) 1 – 2 times daily, intranasally.

Intranasal application of **DDAVP®**:

One dose of the solution provides 0,1 ml, which corresponds to 10 µg desmopressin acetate

The intranasal administration is performed with a plastic catheter (rhinyle tube). The rhinyle tube has a graduated scale corresponding to 2,5 µg, 5 µg, 10 µg, 15 µg and 20 µg desmopressin acetate. As the concentration is 100 µg/ml, the dose can be varied between 0,025 - 0,20 ml. If higher doses are needed it is recommended that these be divided into two doses; the one being given in the left nostril and the other in the right.

Renal concentrating capacity test:

To establish renal concentration capacity, the following single doses are recommended:

- The normal dose for adults is 40 µg;
- for children over 1 year 20 µg;
- for children under 1 year 10 µg.

After administration of **DDAVP®**, any urine collected within one hour is discarded. During the next 8 hours two portions of urine are collected for osmolality testing.

A restricted water intake must be observed (see **Warnings)**

DDAVP® *in nocturnal enuresis:*

The clinical effective intranasal dose varies between patients and ranges between 10 and 20 µg given at the hour of sleep.

The dosage should be established progressively beginning with a 10 µg dose. In case of non-response the daily dose should be increased to 20 µg with a minimal duration of one week. The maximal dose should not exceed 20 µg. A short term treatment period of four to eight weeks is recommended. The recommended dosage may only be administered once in every 24 hours.

A restricted water intake must be observed (see **WARNINGS)**

In the event of signs of fluid retention/hyponatraemia, treatment should be interrupted.

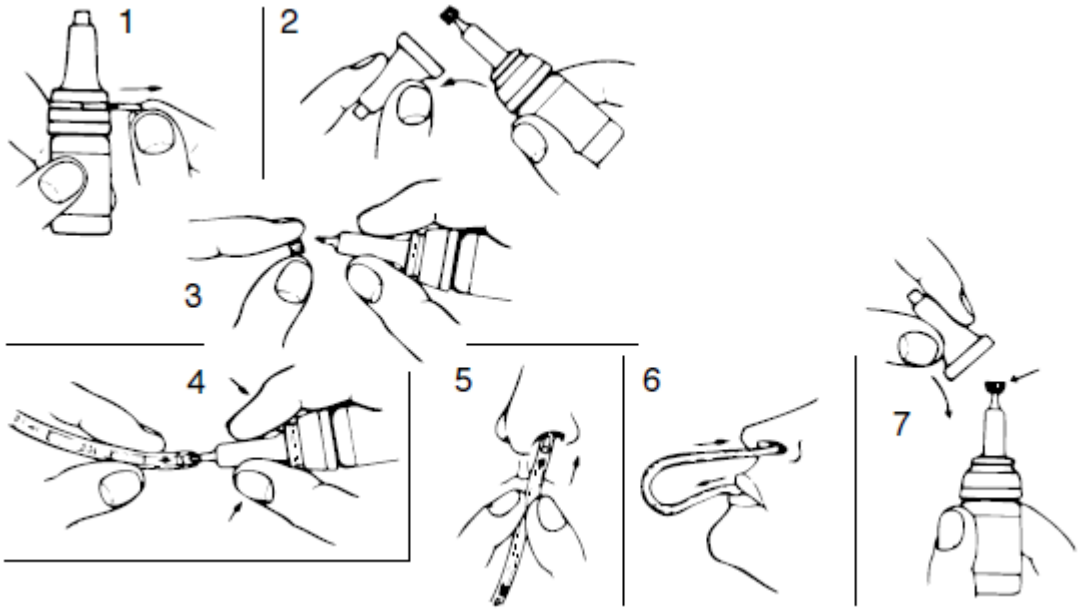
Intranasal application of DDAVP® Intranasal Solution 0,1 mg/ml-Multidose

Directions For Use:

1. Pull plastic tag on neck of bottle.
2. Break security seal and remove plastic cap.
3. Twist of 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. Take the calibrated part of the rhinyle 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 rhinyle 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 rhinyle from the bottle by withdrawing the bottle quickly downwards.

   N.B. In order to prevent air bubbles forming in the rhinyle, maintain constant pressure on the dropper. If difficulty is experienced in filling the rhinyle a diabetic or tuberculin syringe may be used to draw up the dose and load the rhinyle tube.
5. Hold the rhinyle with the fingers approximately 1,5 – 2 cm from the end and insert into a nostril until the tip of the fingers reach the nostril.
6. Put the other end of the rhinyle into the mouth. Hold in breath. Tilt your head back and then blow with a strong puff through the catheter 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 pharynx.
7. After use close the bottle with the plastic cap, wash the rhinyle in water and shake thoroughly, until no more water is left. The rhinyle can then be used for the next application.



SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects:

Treatment without concomitant restriction of water intake may lead to water retention/ hyponatraemia with or without accompanying warning signs and symptoms (headache, nausea/vomiting, reduced serum sodium, weight gain, and, in serious cases, convulsions and coma).

Metabolism and nutrition disorders:

Very rare (≤ 1/10 000): Hyponatraemia.

Psychiatric disorders:

Isolated cases of emotional disturbances in children have been reported but the frequency is unknown.

Respiratory, thoracic and mediastinal disorders:

Common (> 1/100, ≤ 1/10): Nasal congestion/rhinitis, epistaxis.

Gastrointestinal disorders:

Common (> 1/100, ≤ 1/10): Abdominal pain, nausea.

General disorders:

Common (> 1/100, ≤ 1/10): Headache

Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported, but the frequency is unknown.

Excessive doses may cause tachycardia, headaches, mild abdominal cramps, nausea, vomiting, facial flushing, vulva pain and water intoxication from overhydration. In such cases the dosage should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition.

Special Precautions:

Severe bladder dysfunction and outlet obstruction should be considered before starting treatment for primary nocturnal enuresis.

DDAVP® should not be used for enuresis in patients with abnormal renal function.

DDAVP® should not be administered to dehydrated patients until water balance has been largely restored.

Children should be closely observed for possible “water intoxication” due to overingestion of fluids.

Precautions to avoid hyponatraemia, including careful attention to fluid restrictions and more frequent monitoring of serum sodium, must be taken in case of concomitant treatment with drugs, which are suspected to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine and in case of concomitant treatment with NSAID.

Treatment with **DDAVP®** should be interrupted during acute intercurrent illness characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis).

Dosage should be limited to that producing the desired physiological response.

The local absorption of **DDAVP®** in patients with colds has not been established.

DDAVP® should be used with caution in patients with cystic fibrosis.

Pressor effects: Large doses may produce pressor effects in patients and especially in those who are anaesthetised, or who are taking ganglion or adrenergic neurone blockers, or who have defects in sympathetic outflow. Patients with a history of heart disease or hypertension should be treated with caution, and their blood pressure should be monitored.

Since **DDAVP®** is used intranasally, changes in the nasal mucosa, such as scarring, oedema or other disease may cause erratic, unreliable absorption in which case intranasal **DDAVP®**

should not be used.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

At high doses, a transient fall in blood pressure with reflex tachycardia and facial flushing may occur at the time of administration.

There is no known specific antidote for **DDAVP®**. Treatment is symptomatic and supportive. Overdosage increases the risk of fluid retention and hyponatraemia. Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given. Asymptomatic hyponatraemia is treated with discontinuation of desmopressin treatment and fluid restriction. Infusion of isotonic or hypertonic sodium chloride may be added in cases with symptoms. When the fluid retention is severe (convulsions and unconsciousness) treatment with furosemide should be added.

IDENTIFICATION

Clear, colourless solution with an odour of chlorobutanol.

PRESENTATION

Each vial contains 2,5 ml solution (0,1 mg/ml) in amber glass, with a flexible plastic dropper-closure. Two graduated plastic rhinyle tubes (volume marks are indicated on the rhinyle tube from 0,025 to 0,20 ml printed in black) are supplied for accurate intranasal application.

STORAGE INSTRUCTIONS

Store at 2 – 8 °C. Protect from light. Use before expiry date shown. At room temperature (maximum 25 ºC) closed bottles will maintain stability for 4 weeks.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

M/18.2/117

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

30 July 2007

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