PROPOSED FINAL PACKAGE INSERT FOR DDAVP® NASAL SPRAY

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

DDAVP® NASAL SPRAY 0,1 mg/ml (Nasal Spray)

COMPOSITION:

Each ml contains 0,1 mg desmopressin acetate equivalent to 0,089 mg **DDAVP®** (desmopressin) in an isotonic solution adjusted to pH 5.

The solution contains benzalkonium chloride 0,01 % m/v as preservative.

PHARMACOLOGICAL CLASSIFICATION:

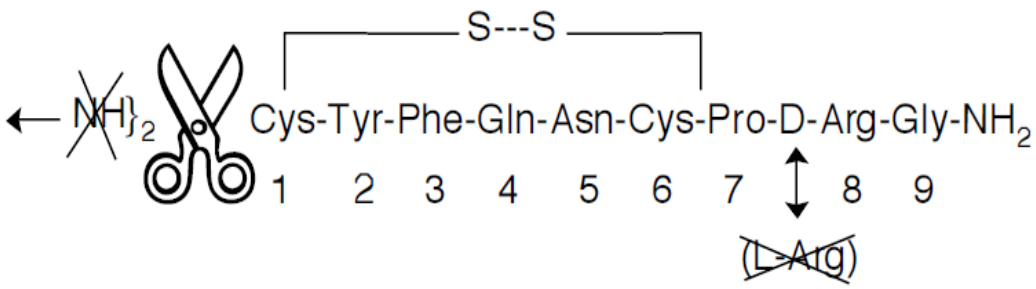
A 18.2 Genito-urinary system – Antidiuretics

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 L-arginine in position 8 has been replaced by D-arginine.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. Then 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 SPECIAL WARNINGS). In normal infants a 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. Syndrome of inappropriate ADH secretion (SIADH)
9. Hypertension.
10. Cerebral vascular disease.
11. Moderate or severe renal insufficiency (creatinine clearance below 50 ml/min).
12. Known hyponatraemia.

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® NASAL SPRAY should be used with caution in:

- Very young and elderly patients
- Conditions characterised by fluid and/or electrolyte imbalance.
- Patients at risk for increased intracranial pressure.

Special Warnings:

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

When **DDAVP®** nasal spray 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.

Due to the presence of benzalkonium chloride this product may cause bronchospasm.

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 high doses 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:

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

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

Dosage is individual. A proposal for normal dosage is**:**

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.

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 also under SPECIAL 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 posology should be established progressively beginning with 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 SPECIAL WARNINGS). In the event of signs of fluid retention/hyponatraemia, treatment should be interrupted.

Intranasal application of DDAVP® NASAL SPRAY 0,1 mg/ml

INSTRUCTIONS FOR USE:

Before **DDAVP®** NASAL SPRAY is used for the first time, prime the pump by pressing downward 4 times or until an even spray is obtained. If the spray has not been used for a week it will be necessary to prime the pump again by pressing it downwards once or until an even spray is obtained.

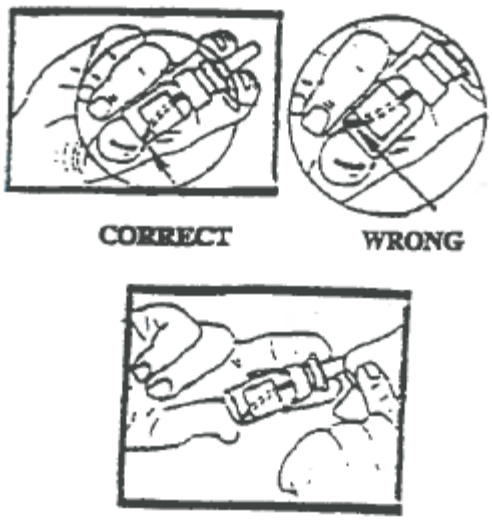
Instructions for use:

The patient should blow his/her nose before using the spray:

1. Remove the protective cap.
2. Control that the end of the tube inside the bottle is submerged in the liquid (see figure).
3. Re-prime the pump if the spray has not been used within the last week.
4. Once primed, the spray delivers 10 μg each time it is pressed.
5. The head must be tipped back slightly while inserting the applicator straight into the nostril.
6. When a higher dose is needed, spray alternatively into each nostril.
7. Replace the protective cap after use and store the bottle in an upright position.

The spray bottle should always be stored in an upright position.

If there is any doubt concerning the correct intake of the dose, the spray should not be re-administered until the next scheduled dose. In young children, administration should be under strict adult supervision to ensure the correct dosage.



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 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 over-ingestion of fluids.

Precautions to avoid hyponatraemia, including careful attention to fluid restriction 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, and 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 neuron 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 diseases 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 a 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.

PRESENTATION:

DDAVP® NASAL SPRAY 0,1 mg/ml contains desmopressin acetate at a concentration of 0,1 mg/ml in a 10 ml injection vial made of amber glass. The vial is equipped with a snap-on, tamper-proof precompression pump, which gives a spray dose of 10 μg desmopressin acetate. The pump outlet is protected by a cap made of polypropylene. Each vial contains either 5 ml or 2,5 ml of **DDAVP®** solution.

STORAGE INSTRUCTIONS:

Store at or below 25 °C

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

U/18.2/99

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

Packed by

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PHARMACEUTICALS

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31 March 2006

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