APPROVED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

DDAVP® Tablet 0,1 mg

DDAVP® Tablet 0,2 mg

COMPOSITION:

DDAVP® Tablet 0,1 mg : Each tablet contains desmopressin acetate 0,1 mg.

DDAVP® Tablet 0,2 mg : Each tablet contains desmopressin acetate 0,2 mg.

PHARMACOLOGICAL CLASSIFICATION:

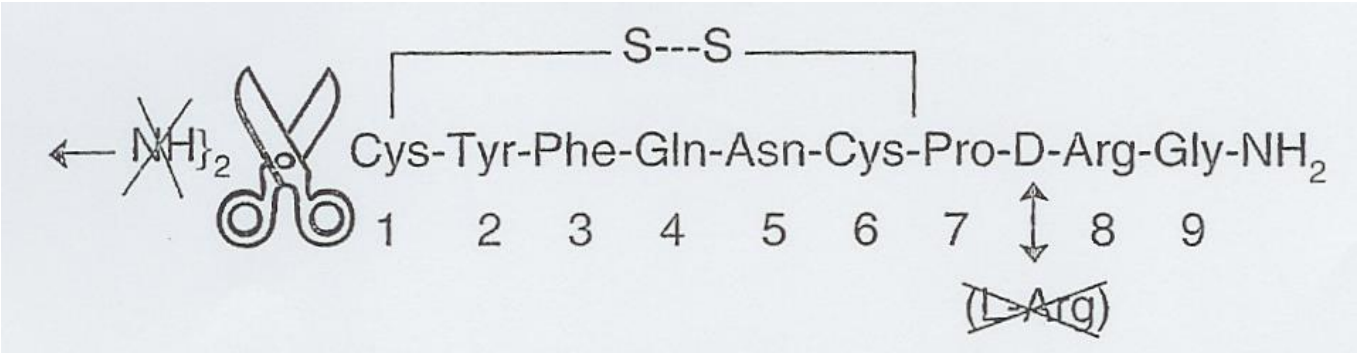
A 18.2 Genito-urinary system - Antidiuretics.

PHARMACOLOGICAL ACTION:

DDAVP® (desmopressin) is a 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 L-Arginine in position 8 has been replaced by D-arginine.



These structural changes result in a compound with increased antidiuretic potency, almost no activity on smooth muscle, hence the avoidance of undesirable pressor side-effects. Oral administration of 0,1 - 0,2 mg desmopressin provides an antidiuretic effect, lasting in most patients for 8 - 12 hours. Relative to intranasal administration, the bio-availability is about 5 %. The kinetics of the 0,1 mg is significantly different from the 0,2 mg.

INDICATIONS:

1. Management of central diabetes insipidus.
2. DDAVP® is indicated for the symptomatic short term (4 - 8 weeks) treatment of primary nocturnal enuresis in children older than 5 years who have normal ability to concentrate urine.

CONTRA-INDICATIONS:

1. Nephrogenic diabetes insipidus.
2. Hypersensitivity to desmopressin or any of the excipients of DDAVP tablets.
3. Pregnancy.
4. Peripheral vascular disease.
5. Cardiac failure or decompensated cardiac insufficiency.
6. Cirrhosis.
7. Nephrotic syndrome and all forms of chronic renal disease.

8. All oedematous states.
9. Hypertension.
10. Cerebral vascular disease.
11. Habitual and psychogenic polydipsia.
12. Patients receiving diuretics.
13. Known hyponatraemia.
14. DDAVP® should not be used for enuresis in patients with abnormal renal function.

WARNINGS:

Children should be closely observed to avoid overingestion of fluid.

When used for primary nocturnal enuresis the fluid intake must be limited and only to satisfy thirst from 1 hour before until 8 hours after administration. Treatment without concomitant reduction of fluid intake may lead to water retention and/or hyponatraemia with or without accompanying warning signs and symptoms (headache, nausea, vomiting, weight gain, and, in severe cases, convulsions).

<u>Interactions with other medicines</u>:

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

Chlorpropamide and clofibrate may prolong the action of DDAVP®. The dosage of DDAVP® may need to be adjusted to avoid hyponatraemia during the concurrent administration of

these agents. Carbamazepine may also prolong the action of DDAVP®.

Non-steroid anti-inflammatory drugs may induce water retention/hyponatraemia.

Glibenclamide: The antidiuretic response induced by DDAVP® has been shown to be significantly reduced by Glibenclamide. In addition the antidiuretic effect of DDAVP® was of significantly shorter duration.

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

Concomitant treatment with loperamide may result in a 3-fold increase of desmopressin plasma concentrations, which may lead to an increased risk of water retention/ hyponatraemia

Desmopressin does not undergo significant liver metabolism in *in vitro* studies with human microsomes and are therefore unlikely to interact with drugs affecting hepatic metabolism. Formal *in vivo* studies have however not been performed.

A standardised 27 % fat meal significantly decreased absorption (rate and extent) of oral desmopressin. No significant effect was observed with respect to pharmacodynamics (urine production or osmolality) hence desmopressin may be taken with food if desired.

PREGNANCY AND LACTATION:

Safety during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Optimal dose of DDAVP® tablets is individually adjusted until the patient is stabilised, including those instances where a patient is switched from any other DDAVP® dosage form to the tablet.

1. Central diabetes insipidus:

A suitable starting dose for adults and children is 0,1 mg three times daily. The dosage regimen should be adjusted in accordance with the patient's response in order to ensure an optimum dose. The total daily dose varies between 0,2 and 1,2 mg. For the majority of the patients the optimal dosage regimen is 0,1 - 0,2 mg three times daily.

2. Nocturnal Enuresis:

A suitable initial dose is 0,2 mg at bedtime. The dose may be increased up to 0,4 mg if the lower dose is not sufficiently effective. A short term treatment period of four to eight weeks is recommended. The recommended dosage may only be administered once in every 24 hours.

The 0,1 mg and 0,2 mg should not be used interchangeably.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

<u>Immune system disorders</u>

Less frequent: Severe allergic reaction.

Nervous system disorders

Less frequent: Headache.

Cases of emotional disturbances in children have been reported, but the frequency is unknown.

Cardiac disorders

Less frequent: Hypertension, transient hypotension and tachycardia

Gastrointestinal disorders

Less frequent: Abdominal or stomach cramps, nausea.

Skin and Subcutaneous Tissue Disorders

Less frequent: Flushing or redness of skin, pain in vulva.

Renal and urinary disorders

Less frequent: Hyponatraemia or water intoxication.

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.

Special Precautions:

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

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. Care should be taken in the elderly.

Precaution to avoid hyponatraemia must be taken in:

- conditions characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, and syndrome of inappropriate ADH secretion),
- conditions requiring concomitant treatment with diuretic agents

DDAVP® at high dosage has resulted in an increase in blood pressure which disappeared with reduction in dosage. DDAVP® should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no known specific antidote for DDAVP®. Treatment is symptomatic and supportive.

Overdosage leads to a prolonged duration of action with an increased risk of fluid retention and hyponatraemia. Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given. Hyponatraemia is treated by discontinuing the desmopressin treatment, fluid restrictions and symptomatic treatment if needed.

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

IDENTIFICATION:

DDAVP® Tablet 0,1 mg: White, oval, convex tablet with a single score, engraved 0,1.

DDAVP® Tablet 0,2 mg: White, round, convex tablet with a single score, engraved 0,2.

PRESENTATION:

DDAVP® Tablet 0,1 mg: 30 tablets in white round HDPE bottles.

DDAVP® Tablet 0,2 mg: 30 tablets in white round HDPE bottles.

STORAGE INSTRUCTIONS:

Store at or below 25 °C in a dry place.

Keep well closed and protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

DDAVP® Tablet 0,1 mg: 29/18.2/0429

DDAVP® Tablet 0,2 mg: 34/18.2/0402

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Ferring (Pty) Ltd.

Route 21 Corporate Park

6 Regency Drive

Irene X30

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

5 June 2002

DDAVP® 0,1 mg tablet:
Namibia S2 Reg No/Nr: 04/18/0849
Botswana S2 Reg No/Nr: BOT1302383A

DDAVP® 0,2 mg tablet:
Namibia S2 Reg No/Nr: 10/18.2/0424
Botswana S2 Reg No/Nr: BOT1302383B