

DESMOSPRAY – RISK OF HYPONATRAEMIA AND CONVULSIONS PHVWP PUBLIC ASSESSMENT REPORT

1. ISSUE

Concern has been raised regarding the safety profile of desmopressin nasal spray (Desmospray) when used in the indication of primary nocturnal enuresis (PNE).

A pharmacovigilance survey performed in France in March 2005 demonstrated that intranasal forms of desmopressin were responsible for the vast majority of severe adverse drug reactions (ADRs), especially hyponatraemia with water intoxication, when used for PNE in France. The review concluded that the risk / benefit profile of the oral formulation is more favourable than the nasal formulation, and therefore it is planned in France that the spray will gradually be replaced by the melt formulation. The PNE indication is also being removed for the nasal spray in France.

In Spring 2005, as a result of spontaneous reports of hyponatraemia in association with desmopressin, the Austrian Ministry of Health issued a letter emphasising the importance of adherence to the approved labelling regarding indication, dosing regimen and precautionary statements.

In the UK the Marketing Authorisation (MA) holder (Ferring Pharmaceuticals Ltd) was requested to provide a risk / benefit assessment for the nasal formulation compared to the oral formulation. This issue was discussed at the Pharmacovigilance Working Party of the Committee on Medicinal Products for Human Use.

2. BACKGROUND

PNE affects approximately 15-20% of 5 year olds, 5% of 10 year olds and 2-3% of adolescents and adults wet the bed at least once a month. The annual spontaneous cure rate is approximately 10-15%.

Desmopressin is a synthetic analogue of vasopressin. It is available in nasal, oral, intravenous and a recently licensed oral melt formulation. The nasal formulations (spray and drops) are indicated for the treatment of PNE, nocturia associated with multiple sclerosis, the diagnosis and treatment of vasopressin-sensitive cranial diabetes insipidus and establishing renal concentration capacity.

The current UK SPC for Desmospray is attached. It contains the following warnings relating to the PNE indication:

- Patients being treated for PNE should be warned to avoid ingesting water while swimming and to discontinue Desmospray during an episode of vomiting and/or diarrhoea until their fluid balance is once again normal.
- When Desmospray is used for the treatment of enuresis or nocturia associated with multiple sclerosis, fluid intake must be limited from 1 hour before until 8 hours after administration.
- Precautions to prevent fluid overload must be taken in:
 - conditions characterised by fluid and/or electrolyte imbalance

- patients at risk for increased intracranial pressure

Section 4.8 contains the following:

Treatment with Desmopressin without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with accompanying symptoms of headache, nausea, vomiting, weight gain, decreased serum sodium and in serious cases, convulsions.

Enuresis alarms are also available for the treatment of PNE and have efficacy equivalent to desmopressin. However they are sometimes considered inconvenient. Nevertheless bedwetting is a benign disease and therefore any treatment prescribed for this condition should have a very low or no risk of serious adverse effects.

3. ASSESSMENT

3.1 Data submitted

3.1.1 Pharmacokinetics (PK)

Desmopressin is absorbed relatively quickly after both oral and intranasal administration resulting in measurable plasma concentrations 15-30 minutes after administration, and maximal concentrations after an hour.

Assessor's comment: The SPC states that the bioavailability of the nasal formulation is 10%, and the oral formulation 0.08-0.16%. Using the SPC data, the nasal spray has 100-fold greater bioavailability than the oral formulation, yet the nasal dose is only 10-fold smaller than the oral dose. This implies that 2µg of a nasal dose will enter the systemic circulation, compared to 0.2µg of an oral dose.

3.1.2 Comparison of oral and intranasal administration

36 males aged 18-45 participated in an open label, randomised, cross over, multiple dose trial comparing plasma concentrations of desmopressin and antidiuretic responses of 3 oral doses of desmopressin (0.1mg, 0.2mg and 0.4mg) with an intranasal dose of 10µg. This study showed high interindividual differences in plasma desmopressin. The PK profile of the 10µg intranasal dose more closely resembled that of the 0.2mg oral dose. Both forms produced sustained urine reduction and osmolality increases. 10µg intranasally resulted in an antidiuretic response equal to the 0.2mg and 0.4mg oral doses, but closest to the latter.

3.1.3 Effect of daytime or night time administration on PK of desmopressin

This study, in which 16 healthy men aged 55-75 years were given oral or intravenous desmopressin, demonstrated that there was no clear evidence to support differences in PK between day or night time administration. The minor differences in terminal half life seen were thought unlikely to be of clinical significance.

3.1.4 Meta-analysis of age and gender effects on PK

There is no indication that age or weight influences the PK of desmopressin. The exposure received after an oral dose of desmopressin leads to identical plasma levels

of desmopressin irrespective of the child's age and weight. Additionally there is no indication that the PK profile is different for children compared to adults.

A meta-analysis performed by the MA holder indicated that there was no gender effect. Some limitations of the analysis were acknowledged but it was concluded that if there are differences associated with gender then these are likely to be small.

3.1.5 Drug-drug interactions

The MA holder claims that a PK interaction between desmopressin and other drugs is likely to be minimal due to its low protein binding and the minimal involvement of the cytochrome system in its metabolism. A PD interaction could occur with NSAIDs resulting in increased fluid retention and causing hyponatraemia. Concomitant use in patients being treated with diuretics used for fluid overload or hypertension is contraindicated.

Assessor's comment: This information is contained in the SPC for Desmospray, along with information regarding concomitant use with substances known to induce SIADH e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine and carbamazepine, as this may cause an additive antidiuretic effect leading to an increased risk of water retention and / or hyponatraemia.

3.2 Overview of efficacy

A total of 766 patients were included in the Phase II/III programme for PNE (of which 107 were in trials comparing the efficacy and safety of the oral and intranasal formulations). The age range was 5-21 years.

The MA holder has presented the results of 2 studies from the literature showing the efficacy of intranasal desmopressin, one compared to the enuresis alarm, however neither study was placebo controlled and neither study used the lower proposed 10µg dose.

The MA holder also presented the results of 2 long term studies with desmopressin nasal spray. Again these studies were not placebo controlled and the doses of desmopressin used were 20-40µg. Desmopressin was reported to be well tolerated.

The MA holder presented the results of 3 studies comparing the oral and nasal formulations. Neither of the first 2 studies demonstrated a difference between the oral and nasal formulations, but again an intranasal dose of 20µg was used. The MA holder points out the usefulness of having 2 formulations so that patients with nasal congestion or those who have difficulty in swallowing tablets can expect the same level of efficacy. Both treatments were well tolerated in this study. Mean body weight increased in the second study during treatment with desmopressin. There was also an insignificant fall in serum sodium in this study (138.5 mmol/L during the placebo period to 137.5 mmol/L during oral treatment and 137.1 mmol/L during intranasal administration). The third study used an intranasal dose of 40µg and showed the efficacy of both treatments but did not present a comparison between the two. One patient in this study had a single low sodium recorded (128 mmol/L), which was normal on repeat test. The initial result was therefore considered to be erroneous.

In their conclusion on the efficacy of desmopressin the MA holder states that there appears to be a dose-response effect in terms of reducing the average number of wet nights. However in terms of the percentage of responsive patients, this effect is less clear. Thus the optimal dose for individual patients with PNE is best determined by increasing the dose progressively.

3.3 Overview of safety

3.3.1 Clinical trials

There was no formalised dose-ranging study at the time of licensing for the PNE indication in the clinical development programme. The MA holder claims that the dose titration schedule applied in clinical trials has proven efficient for the optimisation of the dose.

The MA holder states that no significant side-effects were seen in the short or long term studies described in section 2.2.

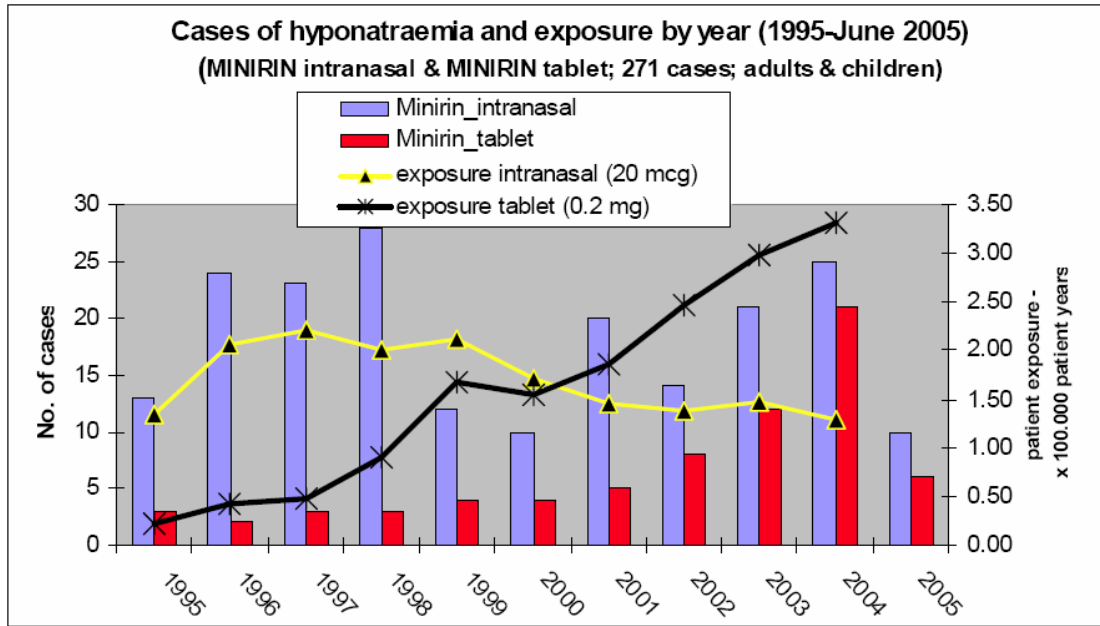
3.3.2 Post marketing data

Bases on sales figures since 1995 it is estimated that 13 million patients have been exposed to desmopressin. The MA holder has assumed that 80% of the sales for the tablet and nasal spray are for the PNE indication. Based on a defined daily dose of 0.2mg for the tablet and 20µg for the spray it is estimated that 5 million children have been exposed to the spray and 5 million to the oral formulation.

The global safety database contains 2158 cases on desmopressin (all formulations), including 87 serious adverse events from clinical trials, 166 from the literature, with the remaining cases being spontaneous reports. 850 reports were considered serious and 1303 non-serious. 409 reports concern the tablet formulation and 1288 were associated with the intranasal formulation.

Since first approval 468 cases of hyponatraemia have been reported for desmopressin. 299 cases (64%) concern the nasal formulation. The MA holder has presented graphs of the number of reports and exposure for each formulation from 1995 to 2005 but has not calculated reporting rates (see figure 1 below).

Figure 1:



Assessor's comment: As a rough estimate for 2004, the reporting rate was 6 per 100,000 patient years of exposure for the tablet formulation compared to 18 for the spray. In 2003 the reporting rate for the tablet formulation was 4 per 100,000 patient years of exposure compared to 13 for the spray. Therefore the reporting rate for hyponatraemia is approximately 3-4 times higher for the spray than the tablet formulation.

The MA holder has presented barcharts on the number of cases of hyponatraemia and exposure by age and year (figures 2 and 3 below). It can be seen that that for the intranasal formulation a greater proportion of cases occur in the younger population (below 18 years). For the tablet formulation the number of cases is lower and the greater proportion of cases occurs in patients greater than 18 years.

Figure 2:

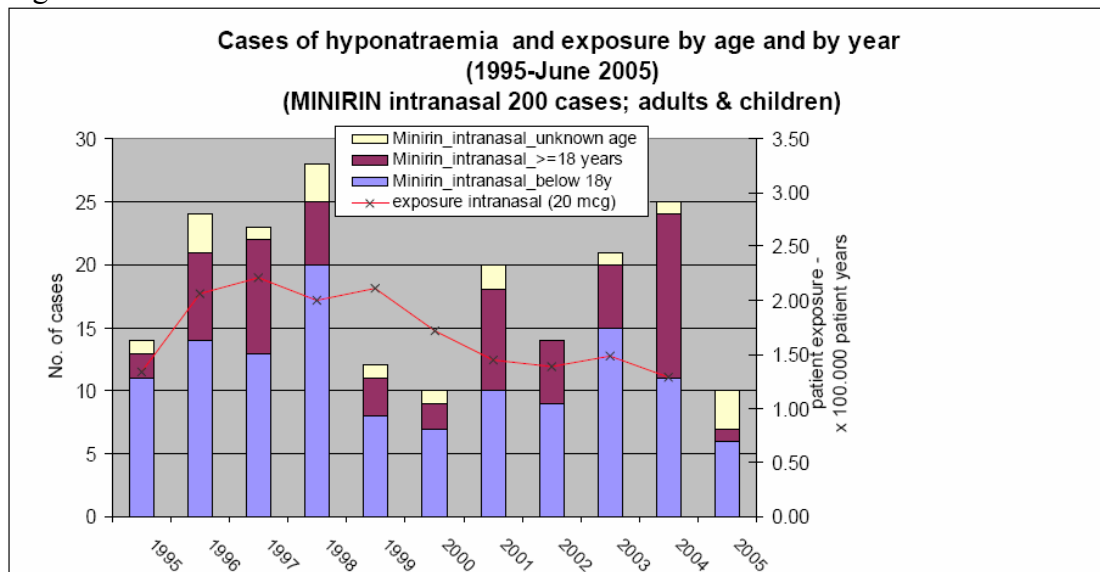
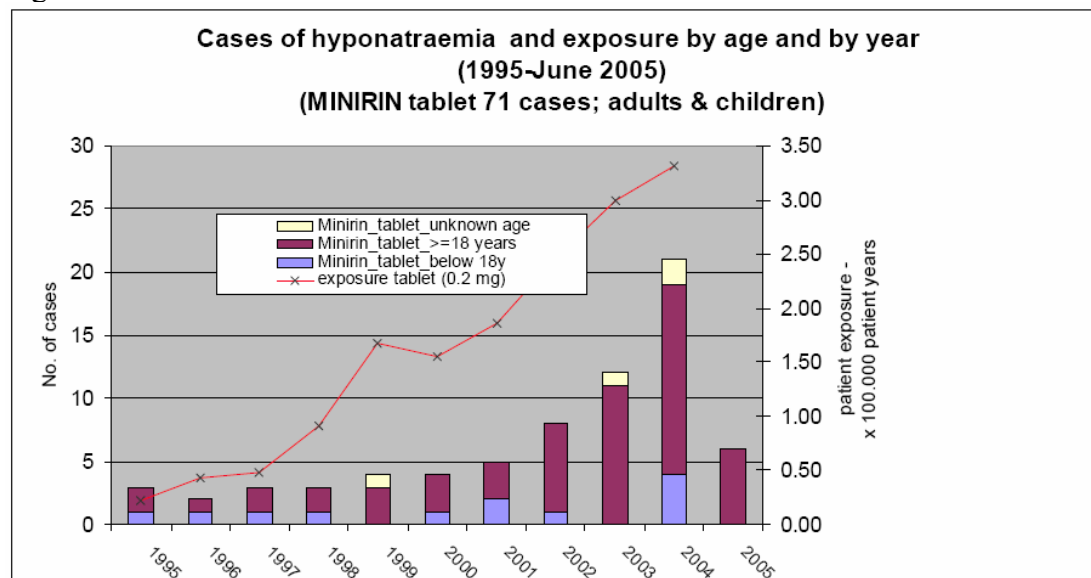


Figure 3:



There have been a total of 299 cases of hyponatraemia reported for Desmospray. 181 (60%) occurred in patients below 18 years. Of the cases in patients below 18 years of age, 145 (80%) occurred in children treated for PNE. Convulsions were reported associated with hyponatraemia in 115 (80%) of these cases. In the majority of cases (41%) the time to onset was within the first 3 days of treatment. Fluid intake was only adequately documented in a few cases. 26% of cases described fluid intake as “increased” or “excessive”. 24% of cases had documented disorders that could potentially increase the risk of water intoxication / hyponatraemia, and 11% of patients were concomitantly treated with oxybutinine which can result in a dry mouth and hence increase fluid intake. 4% of patients also received imipramine which can decrease seizure threshold. 97% of patients were documented as fully recovered. There was one fatal outcome in a 9 year old girl who suffered hyponatraemia and convulsions as a result of extraneous physical activity during warm weather.

Regarding the tablet formulation a total of 71 cases of hyponatraemia have been received with the majority (56%) occurring in the elderly being treated for nocturia. Only 12 cases occurred in children under 18 years, of which 6 were being treated for PNE. Of these 6 cases, 4 were associated with convulsions, and in one of these an overdose was reported. In another 2 cases, other potential risk factors were identified such as concomitant treatment with oxybutinine. All cases fully recovered.

Assessor’s comment: The greater proportion of cases of hyponatraemia seen for Desmospray in the indication of PNE remains a concern. A large proportion of these cases also resulted in a convulsion.

3.3.3 UK ADROIT data

Below is a table showing the number of ADRs of relevant terms (preferred term and higher level terms) received in the UK for desmopressin and for the product Desmospray. This table includes reactions up to 17th March 2006.

Table 1:

	Desmospray	Desmopressin (all formulations)
Blood sodium decreased (PT)	0	1
Blood osmolarity decreased (PT)	1	1
Hyponatraemia (PT)	34	68
Water intoxication (PT)	7	9
Generalised tonic-clonic seizures (HLT)	6	12
Seizures and seizure disorders (HLT)	29	53
Fatal reactions	0	3 (2 cardiac arrest, 1 hyponatraemia)
Total number of reactions	194	449

Assessor's comment: It can be seen from table 1 that the proportion of reactions received for Desmospray is high compared to the number of reactions for all other formulations of desmopressin. This is especially so for the serious outcome of seizures for which more than half of the reactions received were with Desmospray.

4. DISCUSSION

Bedwetting is a benign disease and therefore any treatment prescribed for this condition should have a very low or no risk of serious adverse effects. The data presented shows an unfavourable risk / benefit profile for Desmospray compared to the oral formulation in the PNE indication. The vast majority of cases of hyponatraemia occur with the nasal formulation in the PNE indication, with a large proportion of these reports resulting in the patient having a convulsion.

No data has been presented demonstrating that hyponatraemia and water intoxication are dose-related. Therefore a dose reduction may not prevent the increase in these side effects seen with the nasal formulation.

5. CONCLUSIONS

The conclusions of the Pharmacovigilance Working Party are as follows:

1. Primary nocturnal enuresis should be removed as an indication for nasal spray formulations of desmopressin.
2. A warning of the possible risk of severe hyponatraemia occurring when the spray formulation is used in patients with cranial diabetes insipidus should be included in section 4.4 (Special Warnings & Precautions of Use) of the SPC:

Section 4.4 Special Warnings and Precautions for Use

There is some evidence from post-marketing data for the occurrence of severe hyponatraemia in association with the nasal spray formulation of desmopressin, when it is used in the treatment of cranial diabetes insipidus.

3. The MA holder for Desmospray should propose a risk management plan to closely monitor the safety profile of the melt formulation.

4. The risk and risk minimisation measures should be communicated to paediatricians, urologists and general practitioners.

DESMOSPRAY SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT

DESMOSPRAY[®], Desmopressin Nasal Spray.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Desmospray[®] contains 10 micrograms of Desmopressin acetate per actuation.

3. PHARMACEUTICAL FORM

Nasal spray.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Desmospray[®] is indicated for:

- i) The treatment of primary nocturnal enuresis
- ii) The treatment of nocturia associated with multiple sclerosis where other treatments have failed.
- iii) The diagnosis and treatment of vasopressin-sensitive cranial diabetes insipidus.
- iv) Establishing renal concentration capacity.

4.2 Posology and method of administration

Primary Nocturnal Enuresis:

The starting dose for children (from 5 years of age) and adults (up to 65 years of age) with normal urine concentrating ability who have primary nocturnal enuresis is one spray (10 micrograms) into each nostril (a total of 20 micrograms) at bedtime and only if needed should the dose be increased up to two sprays (20 micrograms) into each nostril (a total of 40 micrograms).

The need for continued treatment should be reassessed after 3 months by means of a period of at least 1 week without Desmospray[®].

Treatment of Nocturia:

For multiple sclerosis patients up to 65 years of age with normal renal function suffering from nocturia the dose is one or two sprays intranasally (10 to 20 micrograms) at bedtime. Not more than one dose should be used in any 24 hour period. If a dose of two sprays is required, this should be as one spray into each nostril.

Treatment of Diabetes Insipidus:

Dosage is individual but clinical experience has shown that the average maintenance dose in adults and children is one or two sprays (10 to 20 micrograms) once or twice daily. If a dose of two sprays is required, this should be as one spray into each nostril.

Diagnosis of Diabetes Insipidus:

The diagnostic dose in adults and children is two sprays (20 micrograms). Failure to elaborate a concentrated urine after water deprivation, followed by the ability to do so after the administration of Desmospray[®] confirms the diagnosis of cranial diabetes insipidus. Failure to concentrate after the administration suggests nephrogenic diabetes insipidus.

Renal Function Testing:

Recommended doses for the renal concentration capacity test:

Adults: Two sprays into each nostril (a total of 40 micrograms)

Children: (1-15 years): One spray into each nostril (a total of 20 micrograms).

Infants (to 1 year): One spray (10 micrograms).

Adults and children with normal renal function can be expected to achieve concentrations above 700mOsm/kg in the period of 5-9 hours following administration of Desmospray[®]. It is recommended that the bladder should be emptied at the time of administration.

In normal infants a urine concentration of 600mOsm/kg should be achieved in the 5 hour period following the administration of Desmospray[®]. The fluid intake at the two meals following the administration should be restricted to 50% of the ordinary intake in order to avoid water overload.

4.3 Contraindications

Desmospray[®] is contraindicated in cases of:

- cardiac insufficiency and other conditions requiring treatment with diuretic agents
- hypersensitivity to the preservative

When used to control primary nocturnal enuresis Desmospray[®] should only be used in patients with normal blood pressure.

Before prescribing Desmospray[®] the diagnoses of psychogenic polydipsia and alcohol abuse should be excluded.

When used to control nocturia in patients with multiple sclerosis, Desmopressin should not be used in patients with hypertension or cardiovascular disease.

Desmopressin should not be prescribed to patients over the age of 65 for the treatment of primary nocturnal enuresis or nocturia associated with multiple sclerosis.

4.4 Special warnings and precautions for use

Care should be taken with patients who have reduced renal function and/or cardiovascular disease or cystic fibrosis.

Patients being treated for primary nocturnal enuresis should be warned to avoid ingesting water while swimming and to discontinue Desmospray[®] during an episode of vomiting and/or diarrhoea until their fluid balance is once again normal.

When Desmospray[®] is used for the treatment of enuresis or nocturia associated with multiple sclerosis, fluid intake must be limited from 1 hour before until 8 hours after administration.

When Desmospray[®] is used in the treatment of nocturia, periodic assessments should be made of blood pressure and weight to monitor the possibility of fluid overload.

When used for diagnostic purposes, fluid intake must be limited and not exceed 0.5 litres from 1 hour before until 8 hours after administration. Following diagnostic testing for diabetes insipidus or renal concentration capacity, care should be taken to prevent fluid overload. Fluid should not be forced, orally or parenterally, and patients should only take as much fluid as they require to satisfy thirst.

Precautions to prevent fluid overload must be taken in:

- conditions characterised by fluid and/or electrolyte imbalance
- patients at risk for increased intracranial pressure

Renal concentration capacity testing in children below the age of 1 year should only be performed under carefully supervised conditions in hospital.

4.5 Interaction with other medicinal products and other forms of interaction



Substances which are known to induce SIADH e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine and carbamazepine, may cause an additive antidiuretic effect leading to an increased risk of water retention and/or hyponatraemia.

NSAIDs may induce water retention and/or hyponatraemia.

4.6 Pregnancy and lactation



Pregnancy:

Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus indicate rare cases of malformations in children treated during pregnancy. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women. Blood pressure monitoring is recommended due to the increased risk of pre-eclampsia.

Lactation:

Results from analyses of milk from nursing mothers receiving high dose Desmopressin (300 micrograms intranasally) indicate that the amounts of Desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.

4.7 Effects on ability to drive and use machines



None

4.8 Undesirable effects



Side-effects include headache, stomach pain, nausea, nasal congestion, rhinitis and epistaxis. Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported. Very rare cases of emotional disturbances in children have been reported. Treatment with Desmopressin without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with accompanying symptoms of headache, nausea, vomiting, weight gain, decreased serum sodium and in serious cases, convulsions.

4.9 Overdose

An overdose of Desmospray® leads to a prolonged duration of action with an increased risk of water retention and/or hyponatraemia.

Treatment:

Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given. Hyponatraemia is treated by discontinuing the Desmopressin treatment, fluid restriction and symptomatic treatment if needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Desmopressin is a structural analogue of vasopressin, with two chemical changes, namely desamination of the N-terminal and replacement of the 8-L-Arginine by D-8-Arginine. These changes have increased the antidiuretic activity and prolonged the duration of action. The pressor activity is reduced to less than 0.01% of the natural peptide as a result of which side-effects are rarely seen.

5.2 Pharmacokinetic properties

Following intranasal administration, the bioavailability of Desmopressin is of the order of 10%.

Pharmacokinetic parameters following intravenous administration have been reported as follows:

Total clearance: 2.6 ml / min / kg body wt.

T_{1/2}: 55mins

Plasma kinetics of DDAVP in man

H Vilhardt, S Lundin, J Falch

Acta Pharmacol et Toxicol, 1986, 58, 379-381

In vitro, in human liver microsome preparations, it has been shown that no significant amount of Desmopressin is metabolised in the liver and thus human liver metabolism *in vivo* is not likely to occur.

It is unlikely that Desmopressin will interact with drugs affecting hepatic metabolism, since Desmopressin has been shown not to undergo significant liver metabolism in *in vitro* studies with human microsomes. However, formal *in vivo* interaction studies have not been performed.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride Ph. Eur.

Citric Acid Monohydrate Ph. Eur.

Disodium Phosphate Dihydrate Ph. Eur.

Benzalkonium Chloride Solution 50% Ph. Eur.

Purified Water Ph. Eur.

6.2 Incompatibilities

None known.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at room temperature (up to 25°C). Protect from light.

6.5 Nature and contents of container

The spray pack comprises of a 10ml amber glass injection vial fitted with a snap-on tamper-proof pre-compression pump spray device, to which a 20mm nasal adaptor is attached. It contains a clear, colourless solution of Desmopressin acetate 0.1mg/ml. The fill volume is 7.1ml including overage to allow delivery of 60 doses of 0.1 ml.

6.6 Instructions for use, handling and disposal

None

7. MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals Limited, The Courtyard, Waterside Drive, Langley, Berkshire SL3 6EZ

8. MARKETING AUTHORISATION NUMBER(S)

PL 3194/0024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30th April 1997

10. DATE OF REVISION OF THE TEXT

September 2002

11. Legal Category

POM

ANNEX 2: Desmopressin nasal spray products marketed in the UK

Licensed Product Name	Authorisation Holder Company Name	Type of Procedure	Product Birth Date (National)
DESMOSPRAY DESMOPRESSION NASAL SPRAY	FERRING PHARMACEUTICALS LIMITED	NATIONAL	01/04/1987
OCTIM NASAL SPRAY	FERRING PHARMACEUTICALS LIMITED	NATIONAL	25/10/2002
ADIURETIN 10 MICROGRAMS/ACTUATION NASAL SPRAY	FERRING PHARMACEUTICALS LIMITED	NATIONAL	07/10/2004
NOCUTIL DESMOPRESSIN 0.1MG/ML NASAL SPRAY	GEBRO PHARMA GMBH	MUTUAL RECOGNITION AT/H/0105/001/IA/023	09/09/1999
DESMOPRESSIN NASAL SPRAY 10MCG/DOSE	ALPHARMA APS	NATIONAL	07/07/2000
DESMOPRESSIN NASAL SPRAY 10MCG/DOSE	ALPHARMA APS	NATIONAL	07/07/2000
DESMOPRESSIN 10 MICROGRAMS PER SPRAY NASAL SPRAY	PLIVA PHARMA LIMITED	NATIONAL	08/04/2003
DESMOPRESSIN SPRAY 10 MICROGRAMS PER SPRAY	PH&T SPA	MUTUAL RECOGNITION UK/H/590/01/E01	28/06/2002
DESMOGALEN 10 MICROGRAMS/ACTUATION NASAL SPRAY	BANQUEM CAPITAL CORPORATION BV	NATIONAL	12/11/2004