A diagnosis of nephrogenic diabetes insipidus should be considered if there is no nocturnal increase in urine output after commencement of desmopressin. Special caution should be exercised in patients taking lithium in case of masking of early-stage lithium-induced nephrogenic diabetes insipidus by administration of desmopressin for a nocturia indication. Desmopressin is not recommended in patients suspected of having lithium-induced nephrogenic diabetes insipidus.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Pharmacodynamic interactions

Substances, which are known to induce SIADH, may cause an increased risk of water retention/hyponatraemia (e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, diuretics and carbamazepine as well as some antipsychotics of the sulfonylurea group, particularly chlorpropamide) (see section Special warnings and precautions for use).

NSAIDs and oxytocin may potentiate the antidiuretic effect of desmopressin and increase water retention/hyponatraemia (see section Special warnings and precautions for use).

Lithium may diminish the antidiuretic effect.

Pharmacokinetic interactions

Concomitant treatment with loperamide may result in a 3-fold increase of desmopressin plasma concentrations following oral administration, which may lead to an increased risk of water retention/hyponatraemia. Although not investigated, other drugs slowing intestinal transport might have the same effect.

A standardised 27% fat meal significantly decreased absorption (rate and extent) compared with desmopressin tablets. The most serious adverse reaction with desmopressin is hyponatraemia, which is associated with headache, nausea, vomiting, decreased serum sodium, weight increase, malaise, abdominal pain, muscle cramps, dizziness, confusion, decreased consciousness and sometimes in severe cases convulsions. Hyponatraemia is an antidiuretic effect, arising from increased water re-absorption by the renal tubules and osmotic diuresis. It is not always due to SIADH (see section Special warnings and precautions for use).

Food intake may reduce the intensity and duration of the antidiuretic effect at low doses of desmopressin (see section Pharmacokinetic properties).

CONTRAINdications

• Hypersensitivity to the active substances or to any of the excipients
• Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/day)
• Known or suspected cardiac insufficiency or other conditions associated with fluid retention
• Insufficient or insufficient to require treatment with diuretics, including a history of such conditions
• Moderate and severe renal insufficiency (creatinine clearance below 50 ml/min)
• Known or suspected epilepsy
• Syndrome of inappropriate ADH secretion (SIADH)

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Pregnancy

Special precautions should be taken to avoid preclinical examination and questioning before commencing treatment with NOCDURNA, given that nocturnal polyuria due to idiopathic nocturnal polyuria and signs of fluid overload. If there is any suspicion of such conditions, treatment with desmopressin is not recommended (see also section Contraindications).

Fluid intake must be limited to a minimum from 1 hour before until 8 hours after administration. Treatment without concomitant reduction of fluid intake may lead to an increased risk of water retention/hyponatraemia. Although not investigated, other drugs slowing intestinal transport might have the same effect.

Fertility

Studies with desmopressin in animals have shown no impairment of fertility in males and female rats.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

NOCDURNA has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Safety profile

Based on the frequency of adverse drug reactions reported in clinical studies with NOCDURNA for nocturia indication conducted in male subjects (50 mcg; N=225) and in female subjects (25 mcg; N=219) the most commonly reported adverse reaction during treatment tablet was dry mouth (13%), headache (5%), hyponatraemia (3%), and dizziness (2%).

Description of selected adverse reactions

Serious adverse reactions observed is hyponatraemia, which is associated with headache, nausea, vomiting, decreased serum sodium, weight increase, malaise, abdominal pain, muscle cramps, dizziness, confusion, decreased consciousness and sometimes in severe cases convulsions. Hyponatraemia is an antidiuretic effect, arising from increased water re-absorption by the renal tubules and osmotic diuresis. It is not always due to SIADH (see section Special warnings and precautions for use).

Females have a higher risk of hyponatraemia which may be due to increased sensitivity of the kidney tubules to vasopressin and its analogues in women with childbearing potential. This risk is minimised by reduction of dose to 25 mcg in women. The risk of hyponatraemia in the over 65 years age group is further reduced by monitoring of serum sodium levels. The majority of the subjects developed low serum sodium within the first three days of treatment or in relation to dose increase. Special attention should be paid to fluid restrictions addressed in section Special warnings and precautions for use.

Tabulated list of adverse reactions

The below table 1 shows the frequencies of adverse reactions reported. The frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and very rare (<1/1,000).

1. Frequency of adverse drug reactions reported (Phase III studies and Post-marketing reports)

<table>
<thead>
<tr>
<th>MedDRA System</th>
<th>Organ Class</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyponatraemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache Dizziness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dry mouth* Nausea Diarrhoea Constipation Abdominal discomfort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue Oedema peripheral</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*It is to be noted that subjects were specifically queried about dry mouth in some of the clinical studies.

OVERDOSE

Symptoms

NOCDURNA leads to a prolonged duration of action with an increased risk of water retention and hyponatraemia.

2009054758
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.

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Vasopressin and analogues.
ATC code: H01B A02
Mechanism of action
NOCDURNA® contains desmopressin a synthetic analogue of naturally occurring anti-diuretic hormone arginine vasopressin (AVP). Desmopressin mimics vasopressin’s anti-diuretic effect, binding to the V2 receptors in the renal collecting tubules of the kidneys, causing reabsorption of water into the body. This reabsorption in turn decreases night-time urine production. Due to the proposed low gender-specific doses (25 mcg for females and 50 mcg for males), and the limited duration of action of NOCDURNA®, the antidiuretic activity is limited to the nighttime sleep period.

Pharmacodynamic effects
In study CS29, the weight-corrected NOCDURNA® dose that induced 50% maximum achievable drug effect on nocturnal urine volume differed significantly between females and males. The estimated exposure value for males was 2.7-fold (95% CI 1.6–3.8) higher than the value for females to obtain an identical dynamic effect, corresponding to higher desmopressin sensitivity among females. The desmopressin half-life of the males was dose dependent. Females are at a higher risk of developing hyponatraemia than males. The incidences of hyponatraemia rises with increasing age (see section Posology and method of administration and Special warnings and precautions for use).

Clinical efficacy
The efficacy of NOCDURNA® has been demonstrated in two randomised double blinded placebo controlled studies in respectively 208 women (study CS40, desmopressin oral lyophilisate 25 mcg versus placebo) and 395 men (study CS41, desmopressin oral lyophilisate 50 mcg and 75 mcg versus placebo) with nocturia defined as an average of ≥2 nocturnal voids per night and polyuria in 90% of women and 87% of men.
Both studies met the 2 co-primary endpoints with statistically significant differences favouring desmopressin oral lyophilisate over the 3-month period. There was a statistically significant decrease in the adjusted mean number of nocturnal voids from the baseline on desmopressin oral lyophilisate 25 mcg (-1.48) compared to placebo (-1.24) in the female study (p=0.028) (Fig. 1) and on desmopressin oral lyophilisate 50 mcg (-1.25) compared to placebo (-0.88) in the male study (p=0.0005) (Fig. 2). The proportion of subjects with >33% decrease in the mean number of nocturnal voids (responders) was significantly increased, nearly doubled. The odds ratio for >33% decrease of desmopressin oral lyophilisate 25 mcg compared to placebo was 1.85 (p=0.006) in the female study and the odds ratio for >33% decrease of desmopressin oral lyophilisate 50 mcg compared to placebo was 1.98 (p=0.0009) in the male study.

For secondary endpoints, there was an increase from baseline to 3 months in the first undisturbed sleep period (FUSP)/time to first void with a treatment contrast of 49 minutes in the female study and 39 minutes in the male study. There was also a statistically significant improvement in quality of life for desmopressin oral lyophilisate 25 mcg (N-QoL total score 27.24) compared to placebo (21.90) (p=0.0226) in female and an improvement for desmopressin oral lyophilisate 50 mcg (N-QoL total score 16.37) compared to placebo (13.88) (p=0.0385) in male. There was a strong association (p=0.0001) in the both studies between treatment response (reduction in number of nocturnal voids and increase in FUSP) and improvements in patients’ quality of life.

Gender differences in clinical safety and efficacy
Clinical study [FE992026 CS029] indicated a dose-response to NOCDURNA® in females and males at doses ranging from 10 to 100 mcg: in females, there was no significant change in pharmacodynamic effect above the dose of 25 mcg, indicating that the dose response plateau was reached at 25 mcg in females. In males, reduction in urine volume was greater at 50 mcg, but not substantially higher at 100 mcg. Increasing doses to 50 mcg dose level in females did not yield further efficacy, being associated with a 5-fold increase in the risk of hyponatraemia compared with males in the age group above 50 years (p = 0.015).

PHARMACOKINETIC PROPERTIES
Absorption
The overall mean absolute bioavailability of desmopressin administered sublingually from earlier dose-ranging studies of doses of 200, 400 and 800 mcg is 0.25%, with a 95% confidence interval of 0.21 – 0.31%. Desmopressin exhibits a moderate-to-high variability in bioavailability, both within and between subjects. Desmopressin shows dose linearity regarding AUC and Cmax in the range of 60 to 240 mcg. However, the bioavailability of doses below 60 mcg has not been evaluated.

Distribution
The distribution of desmopressin is best described by a two-compartment pharmacokinetic model with a volume of distribution during the elimination phase of 0.3-0.5 L/kg.

Biotransformation
The clinical pharmacokinetics of desmopressin has not been studied. In vitro human liver microsome metabolism studies of desmopressin have shown that no significant amount is metabolised in the liver by the cytochrome P450 system. Thus human liver metabolism in vivo by the cytochrome P450 system is unlikely to occur. The effect of desmopressin on the PK of other drugs is likely to be minimal due to its lack of inhibition of the cytochrome P450 drug metabolising system.

Elimination
The total clearance of desmopressin has been calculated to 7.6 L/h. The terminal half-life of desmopressin is estimated to 2.8 hours. In healthy subjects the fraction excreted unchanged was 52 % (44 % - 60 %).

Linearity/non-linearity
There are no indications of non-linearities in any of the pharmacokinetic parameters of desmopressin.

Characteristics in specific groups of patients
Renal impairment
Depending on the degree of renal impairment the AUC and half-life increased with the severity of the renal impairment. Desmopressin is contraindicated in patients with moderate and severe renal impairment (creatinine clearance below 50 ml/min).

Table 2: Pharmacokinetic parameters for different degrees of renal impairment. Data from CS001.

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Renal Function</th>
<th>AUC (Hrs*pg/mL)</th>
<th>T1/2 (Hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy: &gt;80 mL/Mnin</td>
<td>Normal</td>
<td>186</td>
<td>4.0</td>
</tr>
<tr>
<td>Mid: 50-80 mL/Mnin</td>
<td>Mldy impaired</td>
<td>281</td>
<td>8.7</td>
</tr>
<tr>
<td>Moderate: 30-49 mL/Mnin</td>
<td>Moderately imp</td>
<td>453</td>
<td>8.7</td>
</tr>
<tr>
<td>Severe: &lt;29 mL/Mnin</td>
<td>Severely impd</td>
<td>682</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Hepatic impairment
No studies have been performed in this population. It is unlikely that desmopressin will interact with drugs affecting hepatic metabolism, as desmopressin has been shown not to undergo significant liver metabolism in vitro studies with human microsomes.

PRECLINICAL SAFETY DATA
No preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

Carcinogenicity studies have not been performed with desmopressin, because it is closely related to the naturally-occurring peptide hormone.

INCOMPATIBILITIES
Not applicable.

SHELF LIFE
3 years

SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C. Store in the original package in order to protect from moisture and light.

Use immediately upon opening individual tablet blister

NATURE AND CONTENTS OF CONTAINER
Perforated unit dose blisters packed in a carton. The blister bottom foil and the blister lid foil are multilayer laminates consisting of PVC/O/Alu/O/Alu/PVC and heat seal lacquer/Alu/PET/paper, respectively.

Pack size: 5 blisters x 10 oral lyophilisates

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
Instructions for use

1. Completely remove the end tab of a blister strip by tearing along the perforations, starting from the corner with the hand symbol.
2. Now remove one blister from the strip by tearing along the perforations.
3. Place the foil on each blister, starting at the corner with the printed arrow, by peeling off the foil in the direction of the arrow. Do not push the tablet through this hole in the blister.
4. Carefully take a tablet out of its blister. Place the tablet under the tongue and allow it to dissolve. Do not chew or swallow the tablet.
5. If a tablet breaks into more than two pieces while you are taking it out of its blister, do not take the broken pieces. Take a tablet from another blister.

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MANUFACTURER
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