SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Demovo 360 micrograms/ml oral solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the oral solution contains 360 micrograms of anhydrous and acetic-free desmopressin, equivalent to 400 micrograms of desmopressin acetate.

Excipients with known effect:

Sodium methyl parahydroxybenzoate (E-219): 2.1 mg/ml.
Sodium propyl parahydroxybenzoate (E-217): 0.22 mg/ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Demovo 360 micrograms/ml oral solution is indicated in the treatment of central diabetes insipidus and in the treatment of primary nocturnal enuresis in patients (over 5 years) with normal capacity to concentrate urine.

4.2 Posology and method of administration

Posology

Treatment of central diabetes insipidus:

Adults and paediatric population

A suitable starting dose in adults and children is 90 micrograms (0.25 ml) three times daily. The dosage is individually adjusted in diabetes insipidus, but clinical experience has demonstrated that the total daily dose normally lies in the range from 180 micrograms (0.5 ml) to 1080 micrograms (3 ml) of desmopressin. Thereafter, this dosage regimen should then be adjusted in accordance with the patient's response. In most of patients, the maintenance dose is 90-180 micrograms (0.25 – 0.5 ml) three times daily.

If symptoms of fluid retention and/or hyponatremia appear (headache, nausea, vomiting, weight gain, and, in severe cases, seizures), the treatment should be discontinued and the dose of desmopressin should be readjusted.

Primary nocturnal enuresis:

Adults and Children above the age of 5

The appropriate starting dose is 180 micrograms (0.5 ml) of desmopressin at bedtime. The dose may be increased up to 360 micrograms (1 ml) if the lower dose is not effective enough.

Demovo 360 micrograms/ml oral solution is recommended for treatment periods of 3 months. In connection with long-term treatment, a treatment free period of at least one week should be introduced every three months to assess whether spontaneous healing has occurred.

Fluid intake should be controlled.

If symptoms or signs of fluid retention and/or hyponatremia appear (headache, nausea, vomiting, weight gain, and, in severe cases, seizures), the treatment should be discontinued until the patient has recovered. Once again reinstated treatment, fluid intake should be tightly controlled (see section 4.4).

If the desired clinical effect is not achieved after 4 weeks of dose titration, treatment should be discontinued

Treatment of elderly patients (≥65 years of age) should be followed closely due to the increased risk of hyponatremia. Serum sodium should be measured at baseline, three days after onset of treatment or at any dose increase and regularly during prolonged therapy.

Method of administration
Demovo 360 micrograms/ml oral solution is for oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Psychogenic or habitual polydipsia.
- Known or suspected history of cardiac insufficiency.
- Hyponatraemia or predisposition to hyponatraemia.
- Conditions requiring concomitant treatment with diuretic agents (see section 4.5).
- Moderate or severe renal failure (creatinine clearance < 50 ml/min).
- Uncontrolled blood pressure.
- Syndrome of inadequate ADH Production (SIADH) – a condition involving inappropriately high ADH production.

4.4 Special warnings and precautions for use

Special warnings:

In the case of primary nocturnal enuresis, fluid intake shall be limited from 1 hour before administration until the next morning (at least 8 hours).

Treatment without concomitant reduction in water intake may result in fluid retention and/or hyponatraemia with or without warning symptoms and signs (headache, nausea / vomiting, weight gain, and, in severe cases, seizures). See section 4.8.

It is therefore recommended that this danger be pointed out to patients, in particular elderly patients and the parents of young children. Cerebral oedema has repeatedly been reported in children and young adults treated with desmopressin for nocturnal enuresis.

During treatment with desmopressin, body weight, serum sodium and/or blood pressure may have to be monitored.

Care should be taken in patients with reduced renal function and/or cardiovascular disease. In chronic renal disease the antidiuretic effect of Demovo 360 micrograms/ml oral solution would be less than usual.

Precautions for use:

Precautions to prevent hyponatremia shall be taken in:

- conditions characterised by fluid and/or electrolyte imbalance, such as systemic infections, fever, gastroenteritis, and SIADH (syndrome of inappropriate secretion of ADH),
- concomitant treatment with drugs known to induce SIADH, such as tricyclic antidepressants, selective inhibitors of serotonin reuptake, clorpromaxina and carbamazepine,
- concomitant treatment with non steroidal anti-inflammatory drugs (NSAIDs).
- Desmopressin should be used with caution and the dose should be adjusted on the basis of the plasma osmolality in patients with cystic fibrosis
- Serious bladder dysfunction and outlet obstruction should be considered before onset of treatment.
- In patients with urge incontinence, organic causes of increased frequency of micturition or nocturia (e.g. benign prostatic hyperplasia (BPH), urinary tract infection, bladder stones/tumours, bladder sphincter disorders), polydipsia and inadequately controlled diabetes mellitus, the specific cause of the problems should primarily be treated resp. excluded.
- Older people and patients with low serum sodium may have an increased risk of hyponatraemia.

Warnings of excipients:

This product contains sodium methyl (E-219) and sodium propyl (E-217) parahydroxybenzoate. It may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially ‘sodium free’.

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 fluid retention and/or hyponatraemia (see sections 4.3 and 4.4).

NSAIDs may induce fluid retention and/or hyponatraemia (see section 4.4).

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 and/or hyponatraemia.

Concomitant treatment with diuretic agents is contraindicated (see section 4.3)It is unlikely that desmopressin interacts with other drugs which affect liver metabolism, because no significative hepatic metabolism has been observed in *in vitro* studies in human microsomes. However, no formal studies have been conducted *in vivo.*

Concomitant treatment with dimeticone may reduce the absorption of desmopressin.

A standardised 27% greasy meal decreased the absorption of desmopressin (rate and extent). It has not been observed any significant effect on the pharmacodynamics (urine production and osmolality), there is the potential for this to occur at lower

doses. If a diminution of effect is noted, then the effect of food should be considered before increasing the dose.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There is a limited amount of data from the use of desmopressin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Reproductive studies performed in rats and rabbits at doses 100 higher than that recommended in humans did not reveal harmful evidence of desmopressin on foetuses.

Data on a limited number of exposed pregnancies in women treated with desmopressin during pregnancy indicate rare cases of malformations in children. Nonetheless, a review of available data did not suggest an increase of malformations in children exposed to desmopressin during pregnancy. To date, no other relevant epidemiological data are available.

Caution should be exercised when prescribing to pregnant women. Blood pressure monitoring is recommended due to the increased risk of pre-eclampsia (Section 4.3 and 4.4).

The physician should weigh the possible therapeutic advantages against the possible risk in each case.

Breastfeeding:

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

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Demovo 360 micrograms/ml oral solution therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No fertility data available.

4.7 Effects on ability to drive and use machines

Demovo 360 micrograms/ml oral solution has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Treatment without concomitant restriction of fluid intake may result in fluid restriction /hyponatraemia with or without concurrent warning signs or symptoms. The symptoms concerned include headache, nausea/vominitn, reduced serum sodium, weight gain and, in serious cases, convulsions, coma (see section 4.4)

The frequency of adverse events listed below is defined using the following convention:

very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

The most common include headache and gastrointestinal disorders.

Immune system disorders:

Not known: Allergic reactions.

Metabolism and nutrition disorders:

Very rare : Hyponatremia.

Psychiatric disorders:

Very rare : Emotional disturbances.

Nervous system disorders:

Common : headache.

Gastrointestinal disorders:

Common : stomach pain and nausea.

Skin and subcutaneous tissue disorders:

Very rare : Allergic skin reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

An overdose of Demovo 360 micrograms/ml oral solution leads to a prolonged duration of action with an increased risk of water retention and/or hyponatraemia.

Treatment:

Although treatment of hyponatraemia should be adjusted to each patient, the following general recommendations can be followed: hyponatraemia is treated by discontinuing the treatment with desmopressin, fluid restriction and symptomatic treatment, if needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vasopressin and analogues, ATC code: H01BA02.

Desmopressin is a structural analogue of the natural hypophisary hormone arginine vasopressin. They differ in the deamination of the cysteine and substitution of L-arginine by D-arginine. These changes result in a considerable increase in the duration of the antidiuretic effect and a lack of vasopressor effect at clinical doses. In terms of antidiuretic effects, desmopressin is a potent molecule with an EC_{50} value of 1.6 pg/ml. After oral administration, the pharmacological effect may last from 6 to 14 hours.

5.2 Pharmacokinetic properties

Absorption

Desmopressin can be detected in plasma from 15 to 30 minutes after oral administration.

The maximum plasma concentrations are reached after 0.76 hours on average.

The absolute bioavailability of desmopressin administrated orally ranges from 0.08% and 0.16%. The C_{max} was 29.22 pg/ml after administration of 1 ml (360 micrograms) of Demovo 360 micrograms/ml oral solution.

Concomitant food intake reduces the rate and extent of absorption by 40%.

Distribution

The distribution volume of desmopressin is 0.3 l/kg; desmopressin does not cross the blood-brain-barrier, but is excreted in very low quantity into breast milk.

Biotransformation

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

Elimination

65% of the desmopressin orally absorbed can be recovered in the urine within 24 hours. The geometrical mean terminal half-life is 2.5 ± 0.8 hours.

No related to sex differences were observed on the pharmacokinetics of desmopressin.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium methyl parahydroxybenzoate (E-219),

Sodium propyl parahydroxybenzoate (E-217),

Hydrochloric acid (for pH adjustment), and

Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening: 8 weeks.

6.4 Special precautions for storage

Do not store above 30ºC.

Store in the original package.

After first opening the product should be stored below 25ºC for up to 8 weeks

6.5 Nature and contents of container

Amber glass bottles with a low density polyethylene (LDPE) pourer provided with a high density polyethylene (HDPE) screw stopper. The bottle contains 15 ml of solution. The device used for the administration of the oral solution is a 1.5 ml plastic syringe CE marked. The syringe is graduated from 0 to 1.5 ml, with divisions of 0.1 ml. The graduation corresponding to the doses of 0.25 ml, 0.5 ml and 1.0 ml are specifically marked.

Pack size: 1 bottle and one administration device (plastic syringe).

A multi-pack of 3 bottles is also available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

ALTURiX Ltd
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MK9 1EH

8 MARKETING AUTHORISATION NUMBER(S)

PL 44490/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/02/2020

10 DATE OF REVISION OF THE TEXT

04/11/2024