

Physician's Information

NAME OF MEDICINAL PRODUCT

MINIRIN Nasal Spray 0.1 mg/ml

MINIRIN Nasal Solution 0.1 mg/ml

MINIRIN Tablets 0.1 mg

MINIRIN Tablets 0.2 mg

MINIRIN Melt 60 micrograms oral lyophilisate

MINIRIN Melt 120 micrograms oral lyophilisate

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml nasal spray/solution/0.1 mg tablet contains:

Desmopressin acetate 0.1 mg equivalent to Desmopressin 0,089 mg

0.2 mg tablet contains:

Desmopressin acetate 0.2 mg equivalent to Desmopressin 0,178mg

For excipients see section regarding excipients.

60 micrograms oral lyophilisate contains:

60 micrograms desmopressin (as acetate).

120 micrograms oral lyophilisate contains:

120 micrograms desmopressin (as acetate).

PHARMACEUTICAL FORM

Nasal spray/ nasal solution,/tablets/oral lyophilisate

THERAPEUTIC INDICATIONS

Minirin tablets are indicated for Central Diabetes Insipidus, Nocturnal Enuresis (in patients from 5 years of age with normal ability to concentrate the urine) and for symptomatic treatment of nocturia in adults associated with nocturnal polyuria, i.e. nocturnal urine production exceeding bladder capacity.

The treatment must be started before the age of 65.

Minirin nasal spray and solution are indicated for Central Diabetes Insipidus.

Minirin Melt is indicated Nocturnal Enuresis.

POSOLOGY AND METHOD OF ADMINISTRATION

1 dose of the spray provides 0.1 ml, which corresponds to 10 µg desmopressin acetate.

Central Diabetes Insipidus:

Intranasal administration. Dosage is individual. A proposal for normal dosage for adults is 10-20 µg 1-2 times daily. For children 5-10 µg 1-2 times daily.

Tablets administration. A suitable initial dose for children and adults is 0.1 mg three times daily. The dose is then adjusted according to the response of the patient. The average daily dose is between 0.2 and 1.2 mg with tablet administration. For most patients, 0.1 – 0.2 mg three times daily is the optimal dose regimen.

Nocturnal Enuresis:

Tablets administration. 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.

Oral lyophilisate administration

Children over 5 years:

The recommended initial dose is 120 microg at bedtime, administered sublingually. If this dose is not sufficient effective, the dose may be increased up to 240 microg sublingually.

If treatment continues over the long-term, a treatment-free week should be introduced every three months, in order to ascertain whether the condition has resolved spontaneously.

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

Nocturia:

The recommended initial dose is 0.1 mg at bedtime. If this does is not sufficiently effective after one week it can be increased to 0.2 mg and then to 0.4 mg by means of weekly increases. Fluid restriction is to be enforced.

In nocturic patients, a frequency/volume chart should be used to diagnose nocturnal polyuria for at least 2 days and nights before starting treatment. A night-time urine production exceeding the functional bladder capacity or exceeding 1/3 of the 24-hour urine production is regarded as nocturnal polyuria.

Serum sodium must be measured before beginning the treatment and 3 days after initiation or increase in dosage and other times during treatment as seemed necessary by the treating physician.

If adequate medical effect is not achieved within 4 weeks following appropriate dose titration the medication should be discontinued.

Assessment of the necessity of continued treatment should be made after three months during one drug-free week.

Fluid restriction should be observed, (see Special Warnings and Special Precautions for use). In the event of signs of water retention/hyponatraemia treatment should be interrupted.

CONTRA-INDICATIONS

Minirin preparations are contra-indicated in:

- Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours),
- Syndrome of inappropriate ADH secretion (SIADH),
- Known hyponatraemia
- History of known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics.
- Moderate and severe renal insufficiency (creatinine clearance below 50 ml/min).
- Hypersensitivity to desmopressin or to any of the excipients

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

In patients with urgency/urge incontinence, organic causes for increased micturition frequency or nocturia (e.g. benign prostate hyperplasia (BPH), urinary tract infection, bladder stones/tumors), polydipsia and poorly adjusted diabetes mellitus, the specific cause should be treated.

When used for primary nocturnal enuresis and nocturia, the fluid intake must be limited to a minimum from 1 hour before Minirin administration, until the next morning (at least 8 hours) after administration.

Treatment without concomitant reduction in fluid intake can lead to water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and in serious cases convulsions).

In the event of signs or symptoms of water retention and/or hyponatraemia treatment should be interrupted until the patient has fully recovered. When restarting treatment, strict fluid restriction should be enforced.

In clinical trials, higher occurrence of hyponatraemia was found in patients over 65 years. Therefore, the initiation of treatment in the elderly is not recommended, especially not in patients suffering from other conditions that may increase the likelihood of fluid or electrolyte imbalance.

Elderly patients, patients with low serum sodium levels and patients with a high 24-hour urine volumes (above 2.8 to 3 liters) have an increased risk of hyponatraemia.

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.

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.

Treatment with desmopressin should be interrupted during acute intercurrent illness characterized by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis).

Minirin preparations should be used with caution in patients at risk for increased intracranial pressure. Minirin spray/solution should only be used in patients where orally administered formulations are not feasible.

Minirin tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take the tablet dosage form.

Minirin 0.1 mg/ml nasal spray: due to the presence of benzalkonium chloride this product may cause bronchospasm.

When Minirin preparations 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

INTERACTIONS

Substances, which are suspected to induce SIADH, eg. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine, may cause an additive antidiuretic effect leading to an increased risk of water retention/hyponatraemia.

NSAIDs may induce fluid retention and/or hyponatraemia (see *Special Warnings and Precautions for Use* section).

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

Concomitant treatment with dimeticone may result in a decreased absorption of desmopressin.

A standardized meal with 27% fat taken together with or 1.5 h prior to desmopressin decreased the extent and rate of absorption of desmopressin by about 40%. No significant effect was observed with respect to pharmacodynamics (urine production or osmolality). However, it can not be excluded that some patients may have altered effect at concomitant food intake.

PREGNANCY AND LACTATION

Pregnancy

Published 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/foetal 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 µg intranasal), indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None.

UNDESIRABLE EFFECTS

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

Primary nocturnal enuresis & diabetes insipidus

System organ class	Frequency	Adverse event
Immune system disorders	Isolated reports	Allergic reactions
Metabolism and nutrition disorders	Very rare (<1/10,000)	Hyponatraemia
Psychiatric disorders	Very rare (<1/10,000)	Emotional disturbances
Nervous system disorders	Common (> 1/100, <1/10)	Headache
Gastrointestinal disorders	Common (> 1/100, <1/10)	Abdominal pain, nausea
Skin and subcutaneous tissue disorders	Very rare (<1/10,000)	Allergic skin reactions

Nocturia:

In clinical trials in the treatment of nocturia about 35% of the patients experienced adverse drug reactions

during dose-titration. 8% of the patients interrupted in the dose titration phase due to adverse effects and 2% in the subsequent double-blind phase (0.63% on desmopressin and 1.45% on placebo).

System organ class	Frequency	Adverse event
Metabolism and nutrition disorders	Common (> 1/100, <1/10)	Hyponatraemia
Nervous system disorders	Common (> 1/100, <1/10)	Headache, dizziness
Cardiac and vascular disorders	Common (> 1/100, <1/10)	Peripheral oedema
Urinary tract disorders	Common (> 1/100, <1/10)	Micturition frequency
Gastrointestinal disorders	Common (> 1/100, <1/10)	Abdominal pain, nausea, dry mouth, weight increase

Post Marketing: There have been rare reports of thrombotic events (acute cerebrovascular thrombosis, acute myocardial infarction) following the treatment with Desmopressin, causality hasn't been proven yet, but caution should be taken when treating patients with risk factors.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>) or by email (adr@MOH.HEALTH.GOV.IL).

OVERDOSE

Toxicity:

Even normal doses can cause water intoxication (hyponatraemia) in association with a high fluid intake.

Doses exceeding 0.3 ug/kg IV and 2.4 ug/kg intranasally in association with fluid intake have caused hyponatraemia and convulsions in children and adults. However, 40 ug administered intranasally to 5 male children and 80 ug administered intranasally to 5 year-old produced no symptoms. 4 ug administered parenterally to a new-born produced oliguria and weight-gain.

Symptoms:

The same symptoms as for hyponatraemia. Headache, nausea. Fluid retention, hyponatraemia, hypoosmolality, oliguria, CNS depression, convulsions, pulmonary oedema. See also side-effects under "Undesirable effects".

Treatment:

Although the treatment of hyponatraemia should be individualized, the following general recommendations can be given:

Hyponatraemia is treated by interrupting of the desmopressin treatment and restricting fluids. If the patient has symptoms an infusion of isotonic or hypertonic sodium chloride may be given. When the fluid retention is severe (convulsions and loss of consciousness), treat with furosemide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: vasopressin and analogues.

ATC code: HO1B A02

Minirin preparations contain desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in the desamination of cysteine and substitution of L-arginine by D-arginine. This results in a considerably longer duration of action and a complete lack of pressor effect in the dosages clinically used.

Pharmacokinetic properties

After intranasal administration the bioavailability is about 3-5%. Maximum plasma concentration is reached after approximately one hour. An intranasal dose of 10-20 µg provides an antidiuretic effect during 8-12 hours.

The absolute bioavailability of desmopressin after oral administration (tablets) is between 0.08 and 0.16%.

The average maximum plasma concentration is achieved after approximately 2 hours.

The overall mean systemic bioavailability of desmopressin administered sublingually as Melts at doses of 200, 400 and 800 micrograms is 0.25% with a 95% confidence interval of 0.21% - 0.31%. The C_{max} was 14, 30 and 65pg/ml after administration of 200, 400 and 800 micrograms respectively. t_{max} was observed at 0.5 – 2.0 hours after dosing. The geometric mean terminal half-life is 2.8 (CV = 24%) hours.

Correlation table between desmopressin in Tablet and Melt forms:

Tablet	Tablet	Melt	Melt
Desmopressin acetate	Desmopressin free base	Desmopressin free base	Desmopressin acetate
0.1mg	89 micrograms	60 micrograms	Approx. 67 micrograms +
0.2mg	178 micrograms	120 micrograms	Approx. 135 micrograms +
0.4mg	356 micrograms	240 micrograms	Approx. 270 micrograms +

+ calculated for comparative purposes

The bioavailability of desmopressin has a high variability both interindividually and intraindividually.

The distribution volume is 0.3 – 0.32 l/kg.

Desmopressin does not cross the blood brain barrier. Desmopressin transfers into breast milk in very small quantities.

The plasma half-life of desmopressin after intranasal administration is between 2.5 and 4.5 hours, and after oral administration between 2 and 3.21 hours. Around 65% of the desmopressin after oral administration is excreted in the urine within 24 hours.

Preclinical Safety Data

There are no unusual findings during the examination of the safety and safety profile of desmopressin.

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.

PHARMACEUTICAL PARTICULARS

List of excipients

Minirin nasal spray: Sodium chloride, Citric acid monohydrate, Disodium phosphate dihydrate, Benzalkonium chloride, Purified water.

Minirin nasal solution: Sodium chloride, Chlorbutanol hemihydrate, HCl, Purified water.

Minirin tablets: Lactose monohydrate, Potato starch, Povidone, Mg Stearate.

Minirin Melt: Gelatin, Mannitol, Citric acid (anhydrous).

Shelf Life

Minirin nasal spray, tablets and Minirin Melt: 2 years

Minirin nasal solution: 3 years

Storage Conditions

Minirin nasal spray, tablets and Minirin Melt: Store at room temperature not above 25°C and in dry place.

Minirin nasal solution: store between + 2°C to + 8°C.

Nature and contents of container

Minirin nasal spray is actuated by a manual dose pump without propellant. The spray pump is designed to delivery 100 µl solution (=10 µg desmopressin acetate) per dose.

Fill-volume: 5 ml.

Minirin nasal solution: glass bottle equipped with dropper set and rhinyle tube.

Fill-volume: 2.5 ml.

Minirin tablets: HDPE bottles

Minirin Melt: Blisrers.

Instructions for use/handling

Minirin nasal spray. Before Minirin nasal spray is used for the first time, prime the pump by pressing downwards 4 times or until an even spray is obtained. If the spray has not been used for a week, it is necessary to prime the pump again by pressing downwards once or until an even spray is obtained.

When administered it is important that the end of the tube inside the bottle is submerged in the liquid. The head is to be tipped slightly back while inserting the applicator straight into the nostril.

Instructions for use are enclosed with the package.

The spray bottle should always be stored upright.

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.

Minirin nasal solution. The preparation is to be administered according to instructions for use supplied with the package.

Minirin Melt: The oral lyophilisates are brittle and could not be pressed through the foil since they then are running the risk to break. The oral lyophilisates should be taken out from the blisters by removing the aluminium cover.

Manufacturer

Minirin Tablets 0.1 mg & 0.2 mg:

Ferring

Switzerland

Nasal Spray and Nasal Solution and Minirin Melt 60 & 120 micrograms oral lyophilisate:

Ferring GmbH

Germany

License Holder

Ferring Pharmaceuticals Ltd

8, Hashita Street, Industrial Park, Caesarea 38900

Israel

The content of this leaflet was checked and approved by the Ministry of Health in June 2015