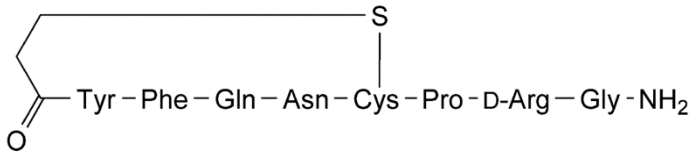
MINIRIN® Tablets

NAME OF THE MEDICINE

Desmopressin Acetate

Synonyms of desmopressin:
DDAVP
1-desamino-8-D-Arginine vasopressin.
Desamino-cys-1-D-Arginine-8 vasopressin.



CAS No (base): 16679-58-6

Molecular weight (base): 1069.22

Physical and chemical characteristics:
A white, fluffy powder, soluble in water, in alcohol and in glacial acetic acid.

DESCRIPTION

Minirin Tablets contain desmopressin, (present as the hydrated acetate with variable amounts of acetic acid and water), a synthetic 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. Minirin Tablets contain desmopressin, lactose, potato starch, povidone and magnesium stearate.

PHARMACOLOGY

Pharmacotherapeutic group: vasopressin and analogues.

Compared to vasopressin, desmopressin has a considerably longer duration of action and a complete lack of pressor effect in the dosages clinically used.

Pharmacokinetics

The absolute bioavailability of orally administered Minirin 200 µg tablets is approximately 0.08% (range 0.029 - 0.115%). Mean maximum plasma concentration is reached within 2 hours. The distribution volume is 0.2 – 0.37 L/kg. Desmopressin does not cross the blood-brain barrier. The oral terminal half-life varies between 2.0 and 3.21 hours. The bioequivalence of the 200 and 400 µg Minirin Tablets has not been established. Desmopressin exhibits a moderate to high variability in bioavailability, both within and between subjects. Concomitant intake of food decreases the rate and extent of absorption of Minirin 200 µg tablets, administered at a dose of 400 µg, by >40%. No significant effect was observed with respect to pharmacodynamics (urine production or osmolality) (see INTERACTIONS WITH OTHER MEDICINES). *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. After iv injection 45% of the amount of desmopressin could be recovered in the urine within 24

hours. No gender related differences in desmopressin pharmacokinetics have been observed.

CLINICAL TRIALS

Cranial diabetes insipidus: Results of 9 published studies in 163 patients demonstrated that diabetes insipidus patients can successfully switch from intranasal to oral treatment. No data are available to suggest that there is an advantage for the oral route over the intranasal dose form although there is a patient preference for the oral form. There is no predictable dose equivalence between intranasal and oral dosing, so individual dose titration is needed (see DOSAGE AND ADMINISTRATION).

Primary nocturnal enuresis: Two double-blind, randomised, placebo controlled studies (RG-84063-607 and RG-84063-609) were conducted in 340 patients, aged 5 to 17 years, with primary nocturnal enuresis. A total of 329 patients were evaluated for efficacy. Patients were evaluated over a two-week baseline period followed by a fixed dose response phase during which patients were randomly assigned to receive 200, 400, or 600 µg of Minirin or placebo for either two weeks (RG-84063-607) or six weeks (RG-84063-609). The primary efficacy variable for both studies was the mean reduction from baseline in the number of wet nights during the final two weeks of treatment (see Table 1 for results).

Table 1:
Summary of Efficacy results (Primary variable – Mean reduction from baseline in number of wet nights during last two weeks of dose-response period) Endpoint Analysis: Intent-To-Treat Patients

RG-84063-607 **Evaluation period: Week 2 (Endpoint)**		Placebo (n=47)	200 µg /day (n=44)	400 µg /day (n=48)	600 µg/day* (n=49)
	Baseline (±SEM)	10 (0.4)	11 (0.4)	10 (0.4)	10 (0.4)
	Reduction from Baseline (±SEM)	1 (0.4)	3 (0.4)	3 (0.5)	4 (0.5)
	Percent Reduction from Baseline	10%	27%	30%	40%
	p-value vs placebo	-	<0.001	<0.001	<0.001
RG-84063-609 **Evaluation period: Week 6 (Endpoint)**		Placebo (n=38)	200 µg /day (n=35)	400 µg /day (n=34)	600 µg /day* (n=34)
	Baseline (±SEM)	11 (0.4)	11 (0.4)	10 (0.5)	11 (0.4)
	Reduction from Baseline (±SEM)	1 (0.6)	2 (0.7)	3 (0.7)	4 (0.7)
	Percent Reduction from Baseline	9%	18%	30%	36%
	p-value vs placebo	-	0.389	0.076	0.006

* This dose is not approved in Australia and is not statistically superior to other doses of desmopressin administered in studies RG-84063-607 and RG-84063-609

Study RG-84063-607 differed in that patients could subsequently enter an ascending dose titration period lasting up to 8 weeks in which patients were randomised to receive either 200 µg of Minirin or Placebo. Patients who were not completely dry at the end of two weeks had their study medication increased in increments of 1 (200 µg) tablet. If required, this titration was repeated at 2 weekly intervals to a maximum of 3 tablets (see Table 2 for results). Whilst some patients treated with 200 µg/day and 400 µg/day of Minirin were completely dry after two weeks, the majority were not and required titration to 600 µg/day.

Table 2:
Summary of Efficacy results (Secondary variable – Mean reduction from baseline in number of wet nights) Endpoint Analysis: Intent-To–Treat Patients

RG-84063-607		Placebo (n=36)	200 µg/day (n=1)	400 µg/day (n=12)	600 µg/day* (n=86)
Evaluation period: Week 8 (Endpoint)	Baseline (±SEM)	11 (0.5)	7 (-)	8 (0.7)	10 (0.3)
	Reduction from Baseline (±SEM)	2 (0.5)	7 (-)	6 (0.9)	3 (0.3)
	Percent Reduction from Baseline	18%	100%	75%	30%
	p-value vs placebo	-	0.388	0.003	0.030

* Dose not approved in Australia.

An uncontrolled long-term study (45A06-62 CESE) was conducted in 294 patients, aged 6-18 years. Those patients (n=256) with a minimum of 10 wet nights during a 28 day observation period were treated with 200 µg/day Minirin for a period of 2 weeks. Those achieving a ≥90% reduction in the number of wet nights (Full response) compared to the observation period were treated for 12 weeks at 200 µg Minirin. The remaining patients were titrated to 400µg/day Minirin for a further 2 weeks and, if they achieved ≥ 50% reduction in the number of wet nights were then treated for 12 weeks at this dose. The other patients were withdrawn from the study. 16 of 253 (6.3%) patients receiving 200 µg Minirin achieved a ≥ 90% reduction in the number of wet nights (Full response). 237 patients received 400 µg Minirin of whom 107 achieved a ≥ 50% reduction in the number of wet nights.

Patients were treated for a year, treatment being stopped for 7 days every 12 week period to allow assessment of the patients for spontaneous remission.
During the 4 blocks of 12-weeks treatment, 24-34% of the patients achieved a >90% reduction in the number of wet nights (Full response) and 41-51% of the patients achieved a ≥ 50% reduction in the number of wet nights (Responder).

INDICATIONS

Minirin Tablets are indicated for the treatment of

- cranial diabetes insipidus
- primary nocturnal enuresis in patients from 6 years of age with normal ability to concentrate urine, who are refractory to an enuresis alarm or in whom an enuresis alarm is contraindicated or inappropriate.

CONTRAINDICATIONS

- Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 mL/kg/24 hours)
- A 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)
- Known hyponatraemia
- Syndrome of inappropriate anti-diuretic hormone secretion (SIADH)
- Hypersensitivity to desmopressin acetate or any of the excipients of Minirin Tablets.

PRECAUTIONS

When used for primary nocturnal enuresis, the fluid intake must be limited to a minimum from 1 hour before administration, until the next morning (at least 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). In the event of signs or symptoms of water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain, and, in severe cases, convulsions) treatment should be interrupted until the patient has fully recovered. When restarting treatment, strict fluid restriction should be enforced. All patients and, when applicable, their guardians, should be carefully instructed to adhere to the fluid restrictions. In the event of signs of water retention/hyponatraemia in cranial diabetes insipidus patients, treatment should be interrupted and the dose should be adjusted.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Severe bladder dysfunction and outlet obstruction should be considered before starting treatment for primary nocturnal enuresis.

Caution should be exercised in patients with other causes of urinary frequency (eg multiple sclerosis or urge incontinence), and in diabetes mellitus and renal impairment, since the use of desmopressin has not been well studied in these populations.

Elderly patients and patients with low serum sodium levels may have an increased risk of hyponatraemia (see USE IN THE ELDERLY).

Precautions to avoid hyponatraemia must be taken in:

- conditions characterised by fluid and/or electrolyte imbalances (such as systemic infections, fever and syndrome of inappropriate ADH secretion (SIADH)) (see CONTRAINDICATIONS)
- conditions requiring concomitant treatment with diuretic agents
- concomitant treatment with drugs known to induce SIADH (see INTERACTIONS WITH OTHER MEDICINES and CONTRAINDICATIONS) including careful attention to fluid restrictions and more frequent monitoring of serum sodium
- concomitant treatment with NSAIDs (see INTERACTIONS WITH OTHER MEDICINES)

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

Precautions must be taken in patients at risk of increased intracranial pressure.

For each approved indication the lowest effective dose should be used. Patient dosage should be reassessed periodically.

Minirin Tablets should be used with caution in patients with cardiovascular disease and the elderly.

Minirin Tablets should not be administered to dehydrated or overhydrated patients until water balance has been adequately restored.

The risk of overhydration including cardiac failure should be borne in mind, especially in children or the elderly or in chronic use.

Minirin Tablets should be used with caution in patients with cystic fibrosis because of impaired water handling and increased risk of hyponatraemia.

Effects on Fertility

Fertility studies have not been done. *In vitro* analysis of human cotyledon models have shown that there is no transplacental transport of desmopressin when administered at therapeutic concentration corresponding to recommended dose.

Use in Pregnancy (Category B2)

Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus as well as data on a limited number (n = 54) of exposed pregnancies in women with von Willebrand disease indicate no adverse effects of desmopressin on pregnancy or on the health of the fetus/newborn child. To date, no other relevant epidemiological data are available.

However, these findings are based on case report data and should be interpreted with caution. No reproduction study has been conducted in animals using oral administration. Studies performed in rats and rabbits with cutaneous doses up to 50ng/kg/day and 10 µg/kg/day, respectively, revealed no evidence for a harmful effect on the fetus.

Caution should be exercised when prescribing to pregnant women.

Use in Lactation

No study has been conducted in animals to examine the effects of desmopressin on postnatal development.

There have been no controlled studies in nursing mothers. In a single dose study in 6 lactating women administered 300 µg desmopressin intranasally, the concentration of desmopressin was less in breast milk than in plasma. However, until further evidence is available for its safe use during lactation, desmopressin should not be used in breast feeding mothers.

Paediatric use

Dose recommendations are the same as in adults. Children should be closely observed to avoid overingestion of fluid and to ensure that only the recommended dose of Minirin Tablet is taken.

Use in the elderly

The initiation of treatment in patients over 65 years of age is not recommended. Should physicians decide to initiate Minirin treatment in these patients then serum sodium should be measured before beginning the treatment and 3 days after initiation or dosage increase, and at other times during treatment as deemed necessary by the treating physician.

Genotoxicity

The genotoxic potential of desmopressin has not been adequately investigated, although *in vitro* studies in bacterial and mammalian cells revealed no mutagenicity of the drug.

Carcinogenicity

The carcinogenic and mutagenic potentials of desmopressin have not been investigated in pre-clinical studies.

Effects on Ability to Drive and Use Machines

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

INTERACTIONS WITH OTHER MEDICINES

- NSAIDs may induce water retention/hyponatraemia (see PRECAUTIONS).
- Substances which are known to release antidiuretic hormone, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine, as well as some antidiabetics of the sulfonylurea group particularly chlorpropamide may cause an additive antidiuretic effect leading to an increased risk of water retention/hyponatraemia
- 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. Although not investigated, other drugs slowing intestinal transport might have the same effect
- 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
- 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). Food intake may reduce the intensity and duration of the antidiuretic effect at low oral doses of desmopressin.

ADVERSE EFFECTS

Treatment with and without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with or without accompanying warning signs and symptoms (headache, nausea/vomiting, weight gain, and in severe cases, convulsions). The risk appears to be dose-related and the elderly (>60 years) are at increased risk.

The most serious adverse reaction with desmopressin is hyponatraemia, which may cause headache, abdominal pain, nausea, vomiting, weight increase, dizziness, confusion, malaise, memory impairment, vertigo, falls and in severe cases convulsions and coma. The cause of the potential hyponatraemia is the anticipated antidiuretic effect. The hyponatraemia is reversible and in children it is often seen to occur in relation to changes in daily routines affecting fluid intake and/or perspiration. In both adults and children special attention should be paid to the precautions addressed in PRECAUTIONS.

Clinical Trials

Cranial diabetes insipidus - During clinical trials with desmopressin in diabetes insipidus the following adverse events have been reported more than once: headache, cold, weight gain, dizziness, sore throat, and depressed mood.

Primary nocturnal enuresis - Adverse Events experienced by at least 2% of exposed patients in CESE (Clinical study of MINIRIN® tablets for PNE)

Patients exposed	256	100%
Adverse Events	161	62.9%
	n	%
RESPIRATORY SYSTEM DISORDERS		
Coughing	34	13.3
Respiratory disorder	26	10.2
Upper resp tract infection	25	9.8
Throat sore	24	9.4
Nasal congestion	10	3.9
Throat infection	9	3.5
Asthma	7	2.7
GASTRO-INTESTINAL SYSTEM DISORDERS		
Vomiting	32	12.5
Abdominal pain	23	9.0
Nausea	22	8.6
Diarrhoea	19	7.4
Cramp abdominal	11	4.3
Gastroenteritis	8	3.1
Stomach upset	7	2.7
BODY AS A WHOLE – GENERAL DISORDERS		
Fever	34	13.3
Influenza-like symptoms	19	7.4
Allergy	8	3.1
CENTRAL & PERIPH NERVOUS SYSTEM DISORDERS		
Headache	51	19.9
SECONDARY TERMS		
Accident and/or injury	20	7.8
RESISTANCE MECHANISM DISORDERS		
Ear infection nos	8	3.1
HEARING AND VESTIBULAR DISORDERS		
Ear ache	10	3.9

Based on the frequency of adverse drug reactions reported in clinical trials with oral desmopressin conducted in children and adolescents for treatment of Primary Nocturnal Enuresis (N = 1923), the following adverse events have been listed:

MedDRA Organ Class	Very common (>10%)	Common (1-10%)	Uncommon (0.1-1%)	Rare (0.1-0.01%)
Immune system disorders	-	-	-	-
Metabolism and nutrition disorders	-	-	-	-
Psychiatric disorders	-	-	Affect lability, Aggression,	(HLT) Anxiety symptoms Nightmare, Mood swings
Nervous system disorders	-	Headache[1)]	-	Somnolence
Vascular disorders	-	-	-	Hypertension
Respiratory, thoracic and mediastinal disorders	-	-	-	-
Gastrointestinal disorders	-	-	Abdominal pain [1)], Nausea [1)], Vomiting [1)], Diarrhoea	-
Skin and subcutaneous tissue disorders	-	-	-	-
Renal and urinary disorders	-	-	(HLT) Bladder and urethral symptoms	-
General disorders and administration site conditions	-	-	Oedema peripheral, Fatigue	Irritability

[1)] Hyponatraemia may cause headache, abdominal pain, nausea, vomiting, weight increase, dizziness, confusion, malaise, memory impairment, vertigo, falls, convulsions and coma.

Post marketing experience

The table below lists additional adverse drug reactions reported in the post marketing period in children, adolescents and adults treated with oral desmopressin, distributed by organ class. The frequency of adverse drug reactions occurring in the post marketing period is regarded as unknown.

MedDRA Organ Class	Not known
Immune system disorders	Anaphylactic reaction
Metabolism and nutrition disorders	Hyponatraemia[1)], Dehydration [2)], Hypernatraemia [2)]
Psychiatric disorders	Abnormal behaviour [3)], Emotional disorder [3)], Depression [3)], Hallucination [3)], Insomnia [3)]
Nervous system disorders	Disturbance in attention [3)], Psychomotor hyperactivity [3)], Convulsions [1)], Asthenia [2)], Coma [1)]
Vascular disorders	-
Respiratory, thoracic and mediastinal disorders	Epistaxis [3)]
Gastrointestinal disorders	-
Skin and subcutaneous tissue disorders	Rash [3)], Dermatitis allergic [3)], Sweating [3)],Urticaria [3)]
Renal and urinary disorders	-
General disorders and administration site conditions	-

[1)] Hyponatraemia may cause headache, abdominal pain, nausea, vomiting, weight increase, dizziness, confusion, malaise, memory impairment, vertigo, falls, convulsions and coma.
[2)] Post marketing reporting in the CDI indication.
[3)] Post marketing reporting in children/adolescents for the PNE indication.

DOSAGE AND ADMINISTRATION

There is no predictable dose equivalence between intranasal and oral dosing, so individual dose titration is needed. If adequate clinical effect is not achieved within 4 weeks following appropriate dose titration, the medication should be discontinued.

For ADH-sensitive Cranial Diabetes Insipidus - Dosage is individualised in diabetes insipidus but clinical experience has shown that the total daily dose normally lies in the range of 200 µg to 1200 µg. A suitable starting dose in adults and children is 100 µg three times daily. The dosage regimen should then be adjusted in accordance with the patient's response. For the majority of patients, the maintenance dose is 100 µg to 200 µg three times daily.

In the event of signs of water retention/hyponatraemia, treatment should be interrupted and the dose should be adjusted (see PRECAUTIONS).

Primary Nocturnal Enuresis - The recommended initial dose is 200 µg at bedtime. If this dose is not sufficiently effective, the dose may be increased up to 400 µg. Fluid intake must be limited to a minimum from 1 hour before until 8 hours after administration.

In the event of signs or symptoms of water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain, and, in severe cases, convulsions) treatment should be

interrupted until the patient has fully recovered. When restarting treatment, strict fluid restriction should be enforced (see PRECAUTIONS).

Minirin Tablets are intended for treatment periods of up to 3 months. The need for continued treatment should be reassessed by means of a period of at least one week without Minirin Tablets.

OVERDOSAGE

Overdose of Minirin Tablets leads to a prolonged duration of action with an increased risk of water 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 restriction and symptomatic treatment if needed.

PRESENTATION AND STORAGE CONDITIONS

Minirin Tablets 100 micrograms desmopressin (as desmopressin acetate). White, oval and convex tablets with a single score and marked “0.1” on one side.

Minirin Tablets 200 micrograms desmopressin (as desmopressin acetate). White, round and convex tablets with a single score and marked “0.2” on one side.

Desmopressin free base represents 89% of the desmopressin acetate content. This is due to the difference in molecular weight as well as the presence of acetic acid/acetate, water and impurities.

MINIRIN Tablets is available in bottles of 30 tablets. Not all strengths are being distributed in Australia.

Store below 25°C. Keep the container tightly closed and do not remove the desiccant capsule from the pack.

NAME AND ADDRESS OF THE SPONSOR

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Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

2 April 2003

DATE OF MOST RECENT AMENDMENT

14 September 2015