VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Bedwetting

Bedwetting (also called primary nocturnal enuresis) is probably the most common developmental problem in children, affecting 15% to 20% of 5-year-olds. By youth 1% to 2% are affected. In a UK study[1], 1260 (15.5%) of 7.5 years olds wet the bed; 12% wet "less than once a week" and 0.8% wet "once a week", thus 82.9% of bedwetting children wet “at most once a week”.

The causes of bedwetting are complex, involving the chemical messengers that send signals from nerve cells (neurotransmitters), the body’s day and night rhythm (circadian rhythm) and bladder function problems. Mortality is not expected by bedwetting.

Condition causing extreme thirst and large volumes of dilute urine (Central Diabetes Insipidus (CDI))

CDI affects 20-30 people per 100,000 inhabitants in all age-groups and both genders. CDI is caused by lack of naturally produced antidiuretic hormone and can be due to brain damage by cancer, lack of oxygen, brain inflammation, cancer treatment, inflammation cells forming lumps (sarcoidosis) or too many of a blood cell type (histiocytosis). Head trauma causes CDI in 15.4% of cases, and 41% in case of open head injury.

Death is not common in the adults. However, severe dehydration, excess of blood sodium (hypernatraemia), fever, too little blood circulation in the body, and death can happen in children, elderly people, or in those with complicating illnesses.

CDI is primarily treated with a drug which acts similar to antidiuretic hormone (desmopressin). The dose of desmopressin is set individually and the dose adjusted according to the patient’s response.

Urinating during the night due to too much night time urine production (Nocturia due to nocturnal polyuria)

It is reported that urinating during the night (nocturia) is the main symptom of excessive night time urine production (nocturnal polyuria (NP)) in up to 75% of patients seeking treatment for bothersome nocturia. The prevalence of nocturia (and especially when due to NP) increases with age and occurs in both genders.

Nocturnal polyuria has been linked to abnormalities of the daily rhythm of (circadian rhythmic) release of naturally occurring antidiuretic hormone.

Nocturia is the most common reason for sleep disturbance, and it can impact both genders and across all age groups. Nocturia due to NP can influence a person’s physical, social and emotional well-being. Literature suggests that disturbances in sleep and metabolism are related.

VI.2.2 Summary of treatment benefits

Bedwetting (Primary nocturnal enuresis (PNE)) and the condition causing extreme thirst and large volumes of dilute urine (central diabetes insipidus (CDI))

[1] Butler, R. J., Golding, J., Northstone, K. and The ALSPAC Study Team (2005), Nocturnal enuresis at 7.5 years old: prevalence and analysis of clinical signs. BJU International, 96: 404–410. doi: 10.1111/j.1464-410X.2005.05640.x

For decades MINIRIN Tablet and MINIRIN Melt (desmopressin) have been used for PNE and CDI. Ferring has not performed classical clinical trials for these uses, but these uses are supported by benefits shown in long clinical experience and published medical literature.

Urinating during the night due to too much night time urine production (Nocturia associated with nocturnal polyuria)
Three clinical trials NOCT-2-A (146 males), NOCT-3-A (142 females), and NOCT-4 (126 both genders)) tested desmopressin in the treatment of frequent night time urination (nocturia) with overproduction of urine during night (nocturnal polyuria) in adults. For 3-weeks, patients received either a dummy treatment (placebo) or desmopressin. In each trial, significantly more patients achieved a 50% decrease in the number of night time voids per night on desmopressin than placebo, both in those below and above 65 years.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns – MINIRIN Melt and Tablets

Important identified risks

Risk	What is known	Preventability
Decreased blood sodium concentration (Hyponatraemia) due to water retention, which could be caused also by overdose.	Decreased blood sodium concentration is a common undesirable effect of MINIRIN Tablet and MINIRIN Melt in adults. The frequency of occurrence in children and adolescents in unknown, as decreased blood sodium concentration has not been reported in clinical trials involving children and adolescents, but only as post-marketing reports. Decreased blood sodium concentration may cause weight gain, headache, nausea and oedema. In severe cases, cerebral oedema, convulsions and coma may occur. When used for primary nocturnal enuresis and nocturia, the fluid intake should be restricted to a minimum from 1 hour before taking MINIRIN Tablet and MINIRIN Melt until 8 hours after taking MINIRIN Tablet and MINIRIN Melt. Treatment without concomitant reduction of fluid intake may lead to water retention and/or lack of sodium in the blood with or without accompanying warning signs and symptoms such as weight gain, headache, nausea, vomiting and formation of oedema. In severe cases cerebral oedema, convulsions and coma may occur.	Yes, it can be avoided by adherence to the recommended initial dosage, by avoidance of the simultaneous administration of substances which promote the secretion of antidiuretic hormone, and when used for primary nocturnal enuresis and nocturia - by following the instructions to limit water/fluid intake while being treated with MINIRIN Tablet and MINIRIN Melt. MINIRIN Tablet and MINIRIN Melt must not be given if the patient has low blood sodium levels (hyponatraemia), drinks unusually large quantities of fluids or experience excessive thirst, has a heart condition or any other disease which require taking of diuretics (medicine helping the body to excrete water and salt), or has moderately or severely reduced kidney function. Details about the symptoms, conditions, other medications and diseased the patient should be aware of are described in the Package Information Leaflet. Some other medicinal products influence the effect of desmopressin. Patients should tell their doctor or pharmacist if they take or have recently taken or consider taking any other medicines. Patients must stop taking this medicine and tell their doctor immediately if they experience one or more of these symptoms: an unusually bad or prolonged headache, confusion, unexplained weight gain, nausea or vomiting.

Risk	What is known	Preventability
	Elderly patients and children under 5 years of age may have an increased risk of hyponatraemia Treatment with desmopressin should be interrupted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis).	Nocturia indication – elderly patients: The initiation of treatment in patients > 65 years is not recommended. Should physicians decide to initiate desmopressin treatment in these patients then serum sodium should be measured before beginning the treatment and 3 days after initiation or increase in dosage and at other times during treatment as deemed necessary by the treating physician.
Allergic reactions and Hypersensitivity (e.g. itching, rash, fever, bronchial spasms and anaphylaxis), including anaphylactic reaction (a strong hypersensitivity reaction that may affect the whole body)	Allergic reactions and hypersensitivity, including anaphylactic reactions have been reported with different desmopressin products. As only post-marketing reports with MINIRIN Tablet and MINIRIN Melt have been received, the frequency of this undesirable effect of MINIRIN Tablet and MINIRIN Melt is not known.	This product will not be given if patients are allergic to desmopressin or any of the ingredients listed in section 6 of the package leaflet

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Blood clots (thrombotic events)	The potential risk of developing blood clots is due to the effect of high doses of desmopressin that may cause clotting after release of coagulation factors in the blood of patients who have other disease(s) and/or risk factors. Blood clots is a very rare side-effect and post-approval data showed approximately three in one million people treated with desmopressin may experience it. Symptoms of blood clots are depending on their size and location may include leg pain, swelling or redness or sudden-onset shortness of breath, chest pain, abnormal heart beats and may be complicated by collapse, shock and heart attack. Disorders of blood coagulation, immobility, oral contraceptives, smoking and injury to blood vessel walls are among the recognised risk factors. Despite the clinical use of desmopressin in haematological indications the mechanisms of action are not completely understood. Desmopressin at very high doses increases the levels of coagulation factors (factor VIII and von Willebrand factor) in the blood. The release is most likely from storage sites. Desmopressin acts on the storage sites via its v2 agonist activity. The recommended doses for MINIRIN Tablet and MINIRIN Melt are much lower than doses needed to influence the coagulation factors.

Missing information

Risk	What is known
Limited data on pregnancy	There is limited information on use of desmopressin in pregnant women. If the patient is pregnant or breast-feeding, thinks she may be pregnant or is planning to have a baby, she should ask her doctor or pharmacist for advice before taking this medicine.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations

for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for MINIRIN Tablet and MINIRIN Melt can be found via the webpage of the national medicinal agencies.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable