VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Nocturnal enuresis or nighttime urinary incontinence, commonly called bedwetting, is involuntary urination while asleep after the age at which bladder control usually occurs. Nocturnal enuresis is considered primary (PNE) when a child has not yet had a prolonged period of being dry. Secondary nocturnal enuresis (SNE) is when a child or adult begins wetting again after having stayed dry. Bedwetting is the most common childhood urologic complaint and one of the most common pediatric-health issues. Most bedwetting, however, is just a developmental delay—not an emotional problem or physical illness. Only a small percentage (5% to 10%) of bedwetting cases are caused by specific medical situations. Bedwetting is frequently associated with a family history of the condition. Most girls can stay dry by age six and most boys stay dry by age seven. By ten years old, 95% of children are dry at night. Studies place adult bedwetting rates between 0.5% to 2.3%.

Diabetes insipidus is a condition characterized by excessive thirst and excretion of large amounts of severely diluted urine, with reduction of fluid intake having no effect on the concentration of the urine. There are several different types of diabetes insipidus, each with a different cause. The most common type in humans is central diabetes insipidus, caused by a deficiency of the antidiuretic hormone (a hormone that reduces the amount of water lost in urine).

Excessive urination and extreme thirst (especially for cold water and sometimes ice or ice water) are typical for diabetes insipidus.

Diabetes insipidus is not the same as diabetes mellitus (sugar diabetes). However, the symptoms are quite similar to those of untreated diabetes mellitus, with the distinction that the urine does not contain glucose and there is no hyperglycemia (elevated blood glucose). Blurred vision is a rarity. Signs of dehydration may also appear in some individuals, since the body cannot conserve much (if any) of the water it takes in.

The extreme urination continues throughout the day and the night. In children, diabetes insipidus can interfere with appetite, eating, weight gain, and growth, as well. They may present with fever, vomiting, or diarrhea. Adults with untreated diabetes insipidus may remain healthy for decades as long as enough water is consumed to offset the urinary losses. However, there is a continuous risk of dehydration and loss of potassium.

The occurrence of diabetes insipidus in the general population is 1 in 25,000 people.

Nocturia, also called nycturia, is the need to get up in the night to urinate, thus interrupting sleep. Its occurrence is more frequent in pregnant women and in the elderly. Nocturia could result simply from too much liquid intake before going to bed (usually the case in the young), coffee or alcohol drinking in the evening. It can be caused by infections of the urinary tract, bladder or prostate problems, heart failure, renal disease or sleep problems. But ageing is generally associated with higher rates of nocturia and an overactive bladder.

In a study in over 4,700 persons nocturia was experienced by 17% of men aged 18-34, 34% of men aged 35-54, 62% of men aged 55-74, and for men over 75 the prevalence was 80%. The figures for women similarly increased with age. Nocturia was noted by 36% of women aged 18-34, by 51%

aged 35-54, by 86% aged 55-74, and by 77% in those aged over 75.
Especially in the elderly nocturia has an impact on quality of life and is often the cause for falls during the night.

VI.2.2 Summary of treatment benefits

Nocutil/Desmopressin Sandoz contains desmopressin acetate, which is an antidiuretic that makes you produce less urine.

Nocturnal enuresis (Bedwetting)
There are a number of treatment and condition management options for bedwetting. Desmopressin treatment is an option with high success rates. The drug replaces the antidiuretic hormone for that night with no cumulative effect. Patients taking desmopressin are 4.5 times more likely to stay dry than those taking a placebo (same product without active substance).
Nocutil/Desmopressin Sandoz tablets are used for treating bedwetting in children over five years following exclusion of organic causes and if other treatments have not helped.

Diabetes insipidus
Central diabetes insipidus is a disease where you produce a lot of urine and get very thirsty because your brain does not produce enough of the hormone that reduces the amount of water lost in urine. The extreme urination continues throughout the day and the night. In children, diabetes insipidus can interfere with appetite, eating, weight gain, and growth, as well. They may present with fever, vomiting, or diarrhea. Adults with untreated diabetes insipidus may remain healthy for decades as long as enough water is consumed to offset the urinary losses. However, there is a continuous risk of dehydration and loss of potassium. The complication of extreme dehydration in children can be severe and life-threatening, so it is important to seek proper medical treatment if diabetes insipidus is suspected.
Nocutil/Desmopressin Sandoz nasal spray and Nocutil/Desmopressin Sandoz tablets are used for treating central diabetes insipidus and lead to a markedly reduced urine excretion rate and better quality of life.

Nocturia
Nocturia is a nighttime incontinence and can be treated by increasing the antidiuretic hormone level with desmopressin.
Nocturia is frequently cited as the cause of nocturnal awakenings leading to sleep loss, daytime fatigue, and reduced quality of life.
Secondarily, the negative impact on quality of life can lead to traumatic falling accidents. Studies with desmopressin show a reduction of visits to the toilet during the night, an improvement of sleep quality and daytime tiredness.

In some countries Nocutil tablets are used for treating nocturia in adults, which is the frequent awakening from sleep at night to pass urine. Currently this indication is not approved in products available in Germany (Nocutil Tabletten) and Netherlands (Desmopressin Sandoz).

VI.2.3 Unknowns relating to treatment benefits

There is no evidence that the efficacy (beneficial effect of the medicinal product) is expected to be different in people regarding their age, sex, race and organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions and hypersensitivity, including anaphylactic reaction	Allergic reactions and hypersensitivity, including anaphylactic reactions, can in rare cases be fatal if adequate medical treatment is not provided. Medication triggered anaphylaxis/anaphylactic reaction can occur in patients of any age; however middle-aged and elderly are particularly susceptible, primarily due to concomitant diseases such as COPD and cardiovascular disease.	The use in patients with hypersensitivity to the active substances or to any of the excipients is contraindicated.
Decreased blood sodium concentration due to water retention, which could be caused also by overdose	Decreased blood sodium concentration with or without fits are considered a well-known issue of desmopressin. Nocutil/Desmopressin Gebro must not be used in patients suffering from low sodium levels in the blood. A special warning is given for not drinking a lot of water or other fluid while using desmopressin. This prevents the body keeping too much	It can be avoided by following the precautions in the labelling and limit the fluid intake as well as the contraindications concerning interaction with other medicinal products.

Risk	What is known	Preventability
	water and losing too much sodium. This is especially important in very young and elderly patients, and in conditions characterised by fluid and electrolyte (salt in the blood) disorders and increased pressure in the brain. Decreased blood sodium concentration may cause headache, nausea, vomiting, weight increase, discomfort, stomach pain, muscle cramps, dizziness, confusion, decreased consciousness and in severe cases convulsions and coma.	

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 with other risk factors. Blood clots is a very rare side-effect and post approval data showed approximately one 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 recognized risk factors.

Missing information

Risk	What is known
Limited data on pregnancy	Not applicable

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable

List of studies in post authorisation development plan

Not applicable

Studies which are a condition of the marketing authorisation (if applicable)

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

The safety concerns were updated in alignment with the outcome of PSUSA/00000964/201412, EMA/PRAC/589834/2015.

As a result, "Anaphylactic reaction/Anaphylactic shock" was removed as an important potential risk and "Allergic reactions and Hypersensitivity" was added as an important identified risk. The term of the important identified risk "Hyponatremia and/or convulsions" was revised in the wording "Overdose, leading to Water retention and Hyponatremia".
It was assessed that the important identified risk "Off label use of the nasal application" can be removed.
"Thrombotic events" was added as an important potential risk and "Limited data on pregnancy" was added as missing information instead of "Children, elderly, pregnant or lactating women and patients with relevant co-morbidities".

Table 3. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
00	24.05.2013	New version	Including response of the RMS
01		PSUSA/00000964/201412, EMA/PRAC/589834/2015	