Desmopressin

16.12.2015 Version 2.0

Public summary of the Risk Management Plan

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Bedwetting
Bedwetting (also called primary nocturnal enuresis, PNE) is probably the most common developmental sickness in children, affecting 15% to 20% of 5-year-olds. By youth 1% to 2% are affected. In a UK study, 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 pathophysiology of bedwetting is complex, involving neurotransmitters, circadian rhythm (low overnight vasopressin level) and bladder function derangements. Mortality is not expected by bedwetting.

Central Diabetes Insipidus (CDI)
CDI is a fairly uncommon disorder. Epidemiological studies showed prevalence of 20-30 patients per 100,000 inhabitants. It affects all age-groups, and both genders. The yearly incidence rate of new cases of CDI was found to be 3 to 4 patients per 100 000. The incidence of (presumable) congenital CDI was found to be 2 infants per 100 000 infants.

CDI is caused by lack of vasopressin and it could occur due to damage to hypothalamus or the pituitary stalk by tumours, anoxia, encephalitis, radiation, sarcoidosis and histiocytosis. Head trauma has been shown to cause CDI in 15.4% of the cases, and as high as 41% in case of penetrating head trauma.

Mortality is rare in the adults. However, severe dehydration, hypernatraemia, fever, cardiovascular collapse, and death can ensue in children, elderly people, or in those with complicating illnesses.

CDI is primarily treated with desmopressin. Desmopressin dosage is individual in CDI and dosage regimen should then be adjusted in accordance with the patient’s response.

Nocturia due to nocturnal polyuria
It is reported that nocturia is the principal clinical manifestation of 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 circadian rhythmic secretion of the endogenous antidiuretic hormone, vasopressin.

Nocturia is the most common reason for sleep disruption, and it can have significant impact in both genders and across all age groups. Nocturia due to NP can have a tangible influence on a person’s physical, social and emotional well-being. Several literatures suggest that disruptions in sleep and metabolic/endocrine function are related.

von Willebrands Disease (vWD)
vWD is the most common inherited bleeding disorder estimated to affect 66-100/million in the general population. The symptoms of vWD are excessive skin bleeding, prolonged oozing after surgical procedures as well as excessive bleeding during menstruation in women.
Acquired von Willebrands Disease is a rare bleeding disorder associated with various underlying diseases and with the use of some medication estimated to affect 0.04-0.2% of the general population.

All age groups and both genders are affected. No estimates are available for death of the disease. Prolonged and extensive bleeding in relation to minor injury / surgery or in relation to menstruation and pregnancy is of major concern. Excessive bleeding during menstruation (defined as > 80 mL of blood loss per menstrual cycle) in women with vWD is affecting 74-92% increasing according to severity of vWD.

Haemophilia A
Haemophilia A is estimated to affect 20/100.000 males varying considerably among countries. It is an inherited sickness only affecting boys. Haemophilia affects individuals from all racial/ethnic backgrounds equally.

In a UK study in 6018 haemophiliacs, death in haemophilia (caused by bleeding and its consequences, liver diseases and Hodgkin disease) exceeded death in the general population. Median life expectancy was 63 years for severe haemophilia and 75 years in mild-moderate haemophilia.

Patients with severe haemophilia (clotting factor less than 1% of normal) suffer frequent (20-30 episodes yearly) and spontaneous bleedings (usually in the muscle or joint). Patients with moderate haemophilia have a factor level of 1-5% of normal. Mild haemophilia (factor level of 6-25% of normal) usually precludes bleeding except after injury or surgery. In 1995, out of 1978 haemophiliacs registered 32% were severely affected, 19% moderately and 49% mildly.

Prolonged bleeding time
Unexpected prolonged bleeding in the perioperative phase in a general surgery population is largely attributable to impaired haemostasis including platelet function and plasma coagulation—either inherited or acquired. Approximately 3–5% of patients who undergo elective surgery suffer from impaired haemostasis with a positive medical history of bleeding (approx. 70% primary and drug-induced haemostatic defect and approx. 30% vWD) that is not detected with the routine coagulation screening tests.

All age groups and both genders are affected. Can be congenital, but most cases are acquired due to the (chronic) intake of non-selective, nonsteroidal analgesics that all implies a high risk of bleeding for acute surgical situations.

VI.2.2 Summary of treatment benefits.

Primary nocturnal enuresis (PNE), central diabetes insipidus (CDI), renal concentration capacity testing, and haematological indications

For several decades desmopressin has been used for treatment of PNE and CDI and later expanded to use for renal concentration capacity testing, and haematological indications. Ferring has not

performed a clinical development program in these indications. The benefit of desmopressin in these indications is supported by the long clinical experience and data published in international medical and scientific literature.

Nocturia associated with nocturnal polyuria

Three short-term (NOCT-2-A (males), NOCT-3-A (females), and NOCT-4 (both genders)) studies were the first to provide efficacy data for desmopressin in the treatment of nocturia associated with nocturnal polyuria. Each short-term study consisted of an open phase to establish the optimal dose for each patient followed by a 1-week treatment break. After the break patients entered a 3-week phase and during this phase patient received either placebo (a dummy treatment) or desmopressin. The number of participants in
[NOCT-2-A], [NOCT-3-A], and [NOCT-4] were 146, 142, and 126 respectively. The primary efficacy endpoint in these studies was the percent of patients with a 50% reduction in the number of nocturnal voids/night. In each study, significantly more desmopressin patients than placebo patients achieved this endpoint (the number of patients reaching the endpoint were from 4.8 to 20.5 times among the groups treated with desmopressin compared to patients receiving placebo).

The primary efficacy endpoint was analysed separately for patients below and above the age of 65 years and
the effect of desmopressin was similar in the two age groups.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hyponatraemia due to water retention, which could be caused also by overdose	Decreased blood sodium concentration is a common side- effect and approximately one in 100 people treated with desmopressin may experience it. 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. However, symptoms may resolve completely without any treatment.	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. MINIRIN tablet and Melt *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, 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.	Addressed in section 4.3 and 4.8: Use in patients with hypersensitivity to the active substances or to any of the excipients is contraindicated

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 recognised risk factors.

Missing information
Limited data on pregnancy.

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.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

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 (including allergic reactions due to fish gelatine in melt formulation)” was removed as a potential risk and “Allergic reactions and Hypersensitivity, including anaphylactic reaction” was added as an important identified risk.

The term of the important identified risk of “Hyponatraemia” was revised. As the proposed wording of “Overdose, leading to water retention and hyponatremia” may inappropriately link hyponatremia only to overdose, to address the conditions where hyponatremia may occur without overdose of desmopressin, the risk of “Hyponatraemia” was revised to “Hyponatraemia due to water retention, which could be caused also by overdose”.

“Limited data on pregnancy” was added as Missing information.