



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Desmopressin

Proprietary Product Name: Nocdurna

Sponsor: Ferring Pharmaceuticals Pty Ltd

November 2017

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Common abbreviations

Abbreviation	Meaning
ADH	Antidiuretic hormone (vasopressin)
AE	Adverse event
ANCOVA	Analysis of covariance
ASA	Australian Specific Annex (to the RMP)
AUC	Area under the curve (plasma)
AUC _{0-∞}	Area under the plasma concentration-time curve from time zero to infinity
AVP	Arginine vasopressin
BBW	Black box warning
BOO	Bladder outlet obstruction
BP	British Pharmacopeia
BPH	Benign prostatic hyperplasia (hypertrophy)
CDI	Central diabetes insipidus
CI	Confidence interval
C _{max}	Maximum plasma concentration
CrCl	Creatinine clearance
DI	Diabetes insipidus
DM	Diabetes mellitus
EMDAC	FDA's Endocrinologic and Metabolic Drug Advisory Committee
EC ₅₀	Concentration at 50% of maximal effect
ED ₅₀	The dose for 50% of the population to obtain the therapeutic effect
eGFR	Estimated glomerular filtration rate
E _{max}	Maximal effect
FAS	Full Analysis Set
FDA	Food and Drug Administration

Abbreviation	Meaning
GLP	Good laboratory practice
GMP	Good manufacturing practice
ICS	International Continence Society
IM	Intramuscular
IV	Intravenous
MedDRA	Medical dictionary for regulatory activities
NMT	Not more than
NOELs	No observable effect levels
NP	Nocturnal polyuria
N-QoL	Nocturia Quality of Life questionnaire
NSAID	Non-steroidal anti-inflammatory drug
OAB	Overactive bladder
ODST	Orally disintegrating sublingual tablet
PAR	Preliminary assessment reports
PASS	Post-authorisation safety study
PD	Pharmacodynamic(s)
Ph.Eur	European Pharmacopeia
PK	Pharmacokinetic(s)
PSUR	Periodic safety update report
QoL	Quality of life
RCCT	Renal concentration capacity testing
RMP	Risk management plan
RMS	Reference member state
SC	Subcutaneously
SIADH	Syndrome of inappropriate antidiuretic hormone secretion

Abbreviation	Meaning
SMQs	Standardised MedDRA queries
SSRI	Selective serotonin reuptake inhibitor
$t_{1/2}$	Elimination half-life
t_{max}	Time to maximum plasma concentration
TCADs	Tricyclic antidepressant (or triple combination antiviral drug)
USP	United States Pharmacopeia

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Major variation (extension of indications, new strength)
<i>Decision:</i>	Approved
<i>Date of decision:</i>	30 November 2016
<i>Date of entry onto ARTG</i>	2 December 2016
<i>Active ingredient:</i>	Desmopressin (as acetate)
<i>Product name:</i>	Nocdurna
<i>Sponsor's name and address:</i>	Ferring Pharmaceuticals Pty Ltd
<i>Dose form:</i>	Wafer
<i>Strengths:</i>	25 µg and 50 µg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	10 and 30 sublingual wafers
<i>Approved therapeutic use:</i>	<p><i>Nocdurna is indicated for the treatment of nocturia due to idiopathic nocturnal polyuria in adults who awaken two or more times each night to void and have not responded to lifestyle measures.</i></p> <p><i>Nocturnal polyuria should be confirmed on the basis of a 24 hour urine frequency volume diary. It is defined as > 33% of urine passed overnight. Secondary causes of nocturia should be excluded (see CONTRAINDICATIONS and PRECAUTIONS).</i></p>
<i>Route of administration:</i>	Sublingual
<i>Dosage:</i>	The treatment regimen is sex specific, involving sublingual administration of 25 µg (women) or 50 µg (men) one hour before bedtime
<i>ARTG numbers:</i>	263596, 264292

Product background

This AusPAR describes the application by Ferring Pharmaceuticals Pty Ltd (the sponsor) to register Nocdurna desmopressin 25 and 50 µg (as acetate) sublingual wafers for the following indication:

Nocdurna is indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void.

Desmopressin is a synthetic analogue of endogenous (pituitary) arginine vasopressin. It is an antidiuretic hormone that prevents excessive water loss in urine. Compared to vasopressin, desmopressin is longer acting, has greater anti-diuretic properties and lacks a pressor effect at clinically relevant doses. Besides the antidiuretic effect, desmopressin has a haematological effect. In higher doses it increases circulating levels of factor VIII and von Willebrand factor.

The standard definition of nocturia is waking up one or more times per night to void, where each voiding episode is preceded and followed by sleep. Treatment is not usually initiated until 2 or more voids per night. Nocturia is a symptom complex associated with several underlying causes and pathologies; it is common in the elderly (occurring in perhaps up to 50% of men and women older than 75 years); and it is one of the most common reasons for sleep disruption.

People with nocturnal polyuria produce larger volumes of urine when asleep, causing them to awaken multiple times in the night to void. The current application is for a change in dosage (new strength) and an extension of indications to include treatment of nocturia due to nocturnal polyuria. The proposed treatment regimen is gender specific; involving sublingual administration of 25 µg for women) and 50 µg for men, one hour before bedtime.

Regulatory status

The product (Nocdurna) received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 2 December 2016.

Desmopressin at the time this application was considered was currently available in Australia in various presentations (intramuscular (IM)/ intravenous (IV) injection, oral tablet, sublingual wafer/melt nasal spray) for several indications as outlined below and in Table 1.

Desmopressin;

Treatment of patients with diabetes insipidus who have a deficiency of endogenous vasopressin (100 to 1,200 µg per day, divided into 2 or 3 doses).

Measurement of the kidney's ability to concentrate urine (that is, renal concentration capacity testing [RCCT]) or patients with suspected renal disease (single dose of 600 µg).

Treatment of children and young adults with primary nocturnal enuresis (200 to 600 µg at bedtime).

To prevent bleeding in patients with haemophilia A or type 1 von Willebrand's Disease (SC injection or a higher dose of nasal spray).

Table 1: Presentations of desmopressin on the ARTG

Tradename	Date of 1st Reg	Abbreviated indications	Dosage
Minirin intranasal solution Dropper bottles, 2.5 mL, 100 µg/mL Minirin injection 4 µg/mL, box of 10 ampoules of 1 mL Octostim injection 15 µg/mL, box of 10 ampoules of 1 mL	1993	Central/cranial diabetes insipidus (CDI) Diagnostic assessment of renal concentrating capacity Mild/moderate haemophilia A	Intranasal: 10 to 40 µg IM/IV: 1 to 4 µg
Minirin nasal spray 6 mL spray pump, delivering 60 doses of 10 µg, intranasal	1997	CDI Nocturnal enuresis 6+ years refractory to alarm or alarm not suitable	10 TO 40 µg
Minirin tablet 100 µg and 200 µg tablets	2003	CDI Nocturnal enuresis 6+ years refractory to alarm or alarm not suitable	100 TO 200 µg x 3 per day 200 TO 400 µg at night
Minirin melt (ODST) 60 µg, 120 µg and 240 µg	2007	CDI Nocturnal enuresis 6+ years refractory to alarm or alarm not suitable	120 to 720 µg in 3 divided doses 120 µg at night

The Australian Product Information (PI) for Minirin tablets and melt state that: "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."

The overseas regulatory status at the time when TGA considered this submission is described below in Table 2.

Table 2: Overseas approval status

Country	Date of Submission/ Intend to submit	Date of Approval	Proposed indication
European Union (decentralized procedure DCP) with reference member state: SE CMSs: AT, BE, BG, CY, CZ, DE, DK, EE, EL, FI, FR, HR, HU, IE, IS,, LI, LT, LU, LV, MT, NL, NO, PT, RO, SE, SI, SK, UK	8 April 2015 (DCP)	21 April 2016	Approved indication: Nocdurna is indicated for symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults.
United States of America	22 June 2009	ongoing	Proposed indication: Nocdurna is indicated for treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void.
Canada	21 December 2011	6 December 2012	Approved indication: Nocdurna is indicated for treatment of nocturia in adults with four or less nocturnal voids
Switzerland	5 July 2016	ongoing	Proposed indication: Nocdurna is indicated for symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults
Singapore	Q4 2016	planned	Proposed indication: Nocdurna is indicated for symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at < <https://www.tga.gov.au/product-information-pi>>.

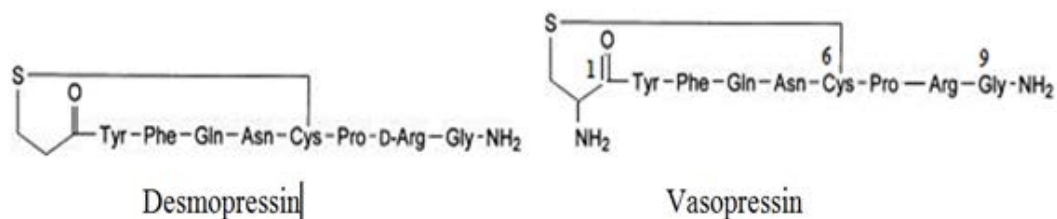
II. Quality findings

Introduction

From the perspective of quality data, this submission is very closely related to the registration of Minirin Melt 60, 120 and 240 µg sublingual wafers as the drug substance as well as the formulations (with the exception of the amounts of desmopressin per wafer) are identical.

Desmopressin is a synthetic polypeptide analogue of the natural pituitary hormone arginine vasopressin. The molecular structures of the two molecules are shown in Figure 1.

Figure 1 Structure of desmopressin and vasopressin



The product is recommended to be administered sublingually without water one hour before bedtime each day, with a 25 µg dose proposed for women and a 50 µg dose proposed for men. The proposed pack sizes are 10 and 30 sublingual wafer blister packs.

Drug substance monographs are available from United States Pharmacopeia (USP), British Pharmacopeia (BP) and European Pharmacopeia (Ph.Eur). The USP drug substance monograph refers to the acetate salt and the BP/Ph.Eur monograph defines the substance as a polypeptide, available as an acetate, meaning it covers both the free base and the acetate salt. Both the USP and the BP include monographs for various desmopressin preparations (USP: injection and nasal spray solution; BP: tablets, injection and intranasal solution). However there was no monograph for desmopressin oral lyophilisate.¹

Drug substance (active ingredient)

The drug substance is identical from a chemistry, manufacturing, quality control and stability perspective to that previously approved for Minirin tablets 100 µg (AUST R 93678) and 200 µg (AUST R 93731) and Minirin Melt wafers containing 60 µg, 120 µg and 240 µg (AUST R's 121720, 121721, and 121722).

Desmopressin is a white to off white fluffy powder, which is soluble in water, in ethanol (96%) and in glacial acetic acid.

The drug substance used in the proposed drug products is manufactured by [information redacted]. The good manufacturing practice (GMP) clearance for [information redacted] is current and acceptable.

The manufacturing and quality control of the drug substance (including the drug substance specification) is acceptable.

¹ A draft monograph for desmopressin oral lyophilisate was published during the time this submission was under consideration

Drug product

The formulations for the two proposed dose strengths 25 µg and 50 µg differ only in the quantity of the drug substance as they are not direct scales and the same quantity of excipients is maintained. The proposed Nocdurna products are also identical to the Minirin Melt products apart from the quantity of the drug substance.

The development and manufacture of the Nocdurna drug products is identical to that used for the registered Minirin Melt 60 µg, 120 µg and 240 µg wafers.

The Nocdurna desmopressin 25 µg and 50 µg wafers are manufactured by [information redacted], with [information redacted] undertaking testing aspects and secondary packaging undertaken by [information redacted]. GMP clearances for the drug product manufacturing sites are acceptable.

Issues concerning the dispensed API container closure system and its transportation have been adequately addressed by the sponsor.

The quality of the drug products is controlled by a specification that includes tests and limits. The proposed expiry limit of 90.0 to 110.0% for the desmopressin assay is wider than those stated in TGO 78 and have been based upon a draft BP monograph for Desmopressin Oral Lyophilisate, which is due to become effective in 2017. An exemption under section 14 of the Act will therefore be required for one year from the date of approval.

The release and expiry limits proposed for the specified impurities [information redacted] and 'Total impurities' in the Nocdurna wafers are identical to those registered for the Minirin Melt sublingual wafers, which have all been toxicologically qualified.

The analytical methods used to analyse the product were adequately described and validated.

The proposed container closure system is for Al/Al blisters within cartons with pack sizes of 10 and 30 wafers proposed for registration. The blister components are identical to those used for the Minirin Melt 60 µg, 120 µg and 240 µg wafers.

The sponsor has requested a shelf life of 48 months when stored below 25 °C in the original container in order to protect from moisture and light.

The product has been found to degrade to some extent on storage and this is related to the amount of water present. [Information redacted].

The sponsor has adequately justified the proposed release and expiry water content limits of [information redacted] and provided additional stability data to support the 48 month shelf life when stored below 25°C.

Biopharmaceutics

Absolute bioavailability

The sponsor referred to an absolute bioavailability study (FE992026 CS004) which was performed using three different doses of desmopressin in oro-dispersible tablets. This study was conducted as part of the submission for Minirin Melt desmopressin sublingual wafers and/or other Minirin dosage forms and has as such been previously evaluated by the TGA as part of those submissions. Consequently, these study reports were accepted in relation to this submission without further evaluation.

Comparative Bioavailability and Bioequivalence studies

- Study FE992026 CS019: study to determine the bioequivalence of a single dose of tablets (2 x 200 µg) and a single lyophilisate wafer (240 µg).
- Study FE992026 CS30: Pharmacodynamics of desmopressin oral lyophilisate wafers compared to desmopressin tablets.

Each of these studies were conducted as part of the submission for Minirin Melt sublingual wafers and/or other Minirin dosage forms and has as such been previously evaluated by the TGA as part of those submissions. Consequently, these study reports were accepted in relation to this submission without further evaluation.

No new biopharmaceutic studies were conducted specifically of the proposed drug product formulations containing 25 µg and 50 µg desmopressin. However, the formulation, manufacture etc. of the proposed products is (apart from the amount of active ingredient) identical to Minirin Melt. Considering that the concentration of active ingredient in both the proposed product and Minirin Melt is very low (below 1.0 %w/w), this was considered acceptable.

Food effect studies

The sponsor has referred to food effect studies submitted previously to support the registration of the Minirin desmopressin 200 µg tablets and the Minirin Melt desmopressin 60 µg, 120 µg and 240 µg sublingual wafers. From those studies, the approved Minirin PI states;

- The overall mean systemic bioavailability of desmopressin administered sublingually as Minirin Melt at doses of 200, 400 and 800 µg is 0.25%.
- Concomitant intake of food decreases the rate and extent of absorption by 40 %.
- A standardised 27% fat meal significantly decreased absorption (rate and extent) of Minirin tablets. 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 Minirin tablets.

The approved PI of Minirin Melt sublingual wafer infers not to take with food rather than stating this categorically.

In comparison, the proposed PI for Nocdurna states:

- The overall mean absolute bioavailability of desmopressin administered sublingually in doses of 200, 400 and 800 µg is 0.25%, with a 95% confidence interval of 0.21 to 0.31%.
- Desmopressin shows dose linearity regarding area under the curve (plasma) (AUC) and maximum plasma concentration (C_{max}) in the range of 60 to 240 µg.
- Bioavailability at doses below 60 µg has not been evaluated.
- There are no indications of non-linearity in any of the pharmacokinetic parameters of desmopressin.
- A standardised 27% fat meal significantly decreased absorption (rate and extent) of desmopressin tablets. 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 tablet.

The food intake warning from the PI of Minirin Melt sublingual wafers is essentially the same as the one in the proposed PI.

The pharmacokinetics section of the proposed PI has no statement that food may reduce bioavailability. Food may reduce the effect of Nocdurna without stating categorically not to take with food.

Quality summary and conclusions

All issues raised with respect to the chemistry and quality aspects of the submission have been adequately resolved and approval is now recommended.

An exemption under section 14 of the Act will be required for one year from the date of approval to allow for assay limits at expiry of 90.0 to 110.0%.

No new biopharmaceutic studies were provided in relation to the proposed lower strength products and the submission only included data previously evaluated for Minirin Melt. The Delegate was asked to consider whether the statements in the draft PI relating to bioavailability (and in particular those relating to the effect of food), which are the same as for Minirin Melt, can be extrapolated to these products.

The application has not been considered by the Pharmaceutical Sub-Committee of the ACPM because no issues requiring their expertise were identified during the chemistry and quality evaluation.

III. Nonclinical findings

Introduction

The application represents an extension of indications for desmopressin.² The proposed treatment regimen is sex specific, involving sublingual administration of 25 µg (women) or 50 µg (men) one hour before bedtime. These doses do not exceed that already approved for the sublingual route (maximum recommended total daily dose of 720 µg with Minirin Melt).

The nonclinical dossier contained new data on pharmacokinetics, repeat dose toxicity and reproductive toxicity, as well as nonclinical studies that were previously submitted and evaluated in applications to register Minirin Melt (Submission No. 2005-1918-5) and Minirin tablets (Appl. No. 94-090-1).

Pharmacology

Desmopressin (1-deamino-8-d-arginine-vasopressin) is a synthetic analogue of the endogenous antidiuretic hormone, arginine vasopressin, and is a selective V2 receptor agonist. V2 receptors are located in the collecting ducts of kidneys where the binding of desmopressin to V2 receptors results in the activation of aquaporins (water channels) in the apical cell membranes of the epithelial cells in the collecting ducts. Urine volume is decreased by aquaporin 2 selectively transporting water from the collecting ducts across

² Desmopressin is currently approved for the treatment of cranial diabetes insipidus, primary nocturnal enuresis, as a diagnostic test to establish renal concentrating capacity, to increase factor VIII levels in patients with haemophilia A or von Willebrand's disease undergoing dental or minor surgery, and treatment of excessive bleeding in patients with platelet dysfunction (Minirin family of products). Approved dosage forms comprise sublingual wafer, tablet, nasal spray and solution for injection.

the cell membrane into the cells which then exits the cells from the basolateral plasma membrane by aquaporin 3 or aquaporin 4 into the blood. The antidiuretic activity of desmopressin has been demonstrated in animal models following intravenous, subcutaneous and oral administration.^{3,4,5,6,7} There are no nonclinical efficacy studies specifically related to nocturia.

Pharmacokinetics

Sublingual administration of desmopressin as a wafer with the oesophagus occluded was shown to be associated with a 5.6 fold increase in bioavailability (based on plasma area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$)), prolonged absorption time (time to maximum plasma concentration (T_{max}) of 1.9 compared with 0.7 hour) and higher peak plasma concentrations (5.8 fold increase in plasma C_{max}) compared with oral administration of desmopressin tablets in a new study conducted in pigs. Without oesophageal occlusion to prevent swallowing, sublingual wafer administration resulted in 3.5 fold higher bioavailability compared with oral administration of tablets. Despite the higher relative bioavailability with sublingual compared with oral administration, absolute bioavailability by the sublingual route is still very low (reported to be 0.25% in humans).

Toxicology

General toxicity

A newly submitted study compared the toxicity of desmopressin oral tablets and sublingual wafers in dogs dosed once daily for 4 weeks. The study was adequately conducted in terms of species selection, duration, group size and the set of endpoints examined, and was good laboratory practice (GLP) compliant. The doses used (400 µg/day orally and 240 µg/day sublingually) resulted in comparable systemic exposure in the two treatment groups, with the plasma AUC in animals approximately 25 times higher than anticipated in patients treated with Nocurna at the maximum recommended dose of 50 µg/day (extrapolating linearly from a human AUC of 85.7 pg·h/mL obtained with sublingual dosing at 240 µg in Clinical Study CS020). No treatment related adverse effects were observed. As expected, based on the drug's pharmacology, treatment with desmopressin reduced urine volume.

Reproductive toxicity

Desmopressin had no adverse effect on male or female fertility in a newly submitted study in rats involving treatment at doses up to 200 µg/kg/day subcutaneously (SC).

³ Vávra et al., 1968 Effect of a synthetic analogue of vasopressin in animals and in patients with diabetes insipidus. *Lancet* 1:948–952.

⁴ Johnson et al., 1979 Effects of AVP and DDAVP on plasma renin activity and electrolyte excretion in conscious dogs. *Am. J. Physiol.* 236:F66–F70.

⁵ Škopková et al., 1981 Comparison of antidiuretic and natriuretic effects of [8-lysine]vasopressin and [8-D-arginine]deaminovasopressin in conscious rats. *Endocrinol. Exp.* 15:129–138.

⁶ Beck et al., 1982 Desamino-D-arginine vasopressin induces fatty acid cyclooxygenase activity in the renal medulla of diabetes insipidus rats. *J. Pharmacol. Exp. Ther.* 221:269–274

⁷ Vilhardt H. and Bie P. 1984 Antidiuretic effect of perorally administered DDAVP in hydrated humans. *Acta Endocrinol.* 105:474–476.

Two embryofetal development studies, conducted by the SC route in rats and rabbits, were evaluated previously.^{3,8} No adverse effects on embryofetal development were seen in either species up to the highest dose levels tested (0.05 µg/kg/day in rats and 10 µg/kg/day in rabbits). Two further embryofetal development studies were included in the submission, and investigated higher doses of desmopressin. Again, no adverse effects on embryofetal development were observed in either rats or rabbits up to the highest doses tested (241 µg/kg/day IV in rats; 200 µg/kg/day SC in rabbits).

In a newly submitted pre-/postnatal development study in rats,⁹ maternal treatment with desmopressin at 200 µg/kg/day SC during gestation and lactation was associated with decreased pup birth weight and inhibition of postnatal body weight gain in both sexes, and delayed sexual maturation (vaginal opening) in females. These effects occurred in the absence of maternotoxicity and are seen to be associated with decreased consumption of maternal milk. There were no effects on pup development observed with treatment at 20 µg/kg/day SC.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2.¹⁰ This matches the existing categorisation for desmopressin with the Minirin family of products. Category B2 is for drugs where “studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage”. For desmopressin, the limitation in the animal program relates to dose selection in the previously evaluated rat embryofetal development study;³ the highest dose tested (0.05 µg/kg/day SC) is expected to have resulted in exposure well below the maximum anticipated in humans (for example, noting that twice daily dosing with desmopressin at 0.4 µg/kg IV is countenanced in patients with mild to moderate haemophilia A and von Willebrand’s disease).

The new embryofetal development studies have now established safety in laboratory animal species at doses close to 5,000 times (rats) and 20 times (rabbits) higher than previously shown. While the studies did not include toxicokinetic analyses, very large multiples of the clinical exposure are expected to have been obtained at the No observable effect levels (NOELs) based on cross species comparison of doses adjusted for body surface area and considering the greater bioavailability by the routes used in animals compared with humans. This applies to this product; where the no-effect doses in rats and rabbits are 88 and 145 times higher than the maximum recommended dose of desmopressin with Nocturna therapy in women (25 µg/day sublingually); and all other existing desmopressin products (for example, the NOELs are 55 to 90 times higher than the maximum recommended IV dose [0.8 µg/kg/day; Minirin]).¹¹

⁸ Tucker 1972, Desamino- D-Arginine Vasopressin - Teratology Study in the Rabbit (Study report in nonclinical dossier)

⁹ Naya 1995, Reproductive and developmental toxicity study of KW-8008. Teratogenicity study in rabbits. (Study report in nonclinical dossier)

¹⁰ Pregnancy Category B2 is defined as: “*Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.*

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.”

¹¹ Calculated using µg/kg to µg/m² conversion factors of 6 for rats, 12 for rabbits and 33 for humans, with 50 kg patient body weight assumed as a conservative measure.

Accordingly, the new data resolve the previous deficiencies in the embryofetal toxicity program for desmopressin, and allow reassignment of desmopressin from Pregnancy Category B2 to B1.¹²

Nonclinical summary and conclusions

- The nonclinical dossier contained new data on pharmacokinetics, repeat dose toxicity and reproductive toxicity.
- Desmopressin is a synthetic analogue of arginine vasopressin. Anti-diuretic activity has been demonstrated for desmopressin by various routes and in multiple laboratory animal species. The assessment of efficacy specific to the new indication relies on clinical data only though.
- A new pharmacokinetic study in pigs showed absorption of desmopressin across the oral mucosa following sublingual administration as a wafer formulation. Bioavailability by the sublingual route was multiple times higher than that for orally administered tablets, especially when the oesophagus of the animals was occluded to prevent swallowing.
- The dose of desmopressin with Nocdurna (25 µg/day for women and 50 µg/day for men) does not exceed that already approved for the sublingual route (that is, 720 µg/day with Minirin Melt).
- A four week repeat dose toxicity study comparing the toxicity of desmopressin by the sublingual and oral routes in dogs was submitted, with no treatment related adverse effects seen. The doses tested (240 µg/daily sublingually and 400 µg/day orally) yielded comparable systemic exposure in animals by the two routes, being a very high multiple (approximately 25 times) of the plasma AUC expected in patients at the maximum recommended dose of Nocdurna.
- Desmopressin had no adverse effects on fertility in rats (at doses up to 200 µg/kg/day SC), and no adverse effects on embryofetal development in rats (up to 241 µg/kg/day IV) or rabbits (up to 200 µg/kg/day SC) in newly submitted studies. Decreased pup birth weight, inhibition of postnatal body weight gain and delayed female sexual maturation were observed in a new pre/postnatal development study in rats dosed at 200 µg/kg/day SC.
- The new embryofetal development studies were adequately conducted and used much higher doses than tested in previously evaluated studies. They allow reassignment of desmopressin from Pregnancy Category B2 to B1.
- There are no nonclinical objections to the registration of Nocdurna for the proposed indication.

The nonclinical evaluator also made recommendations relating to the PI but these are beyond the scope of the AusPAR.

¹² Pregnancy Category B1 is defined as: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.*

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Desmopressin

Desmopressin is a synthetic analogue of endogenous (pituitary) arginine vasopressin. It is an antidiuretic hormone that prevents excessive water loss in urine. Compared to vasopressin, desmopressin is longer acting, has greater anti-diuretic properties and lacks a pressor effect at clinically relevant doses.

Besides the antidiuretic effect, desmopressin has a haematological effect. In higher doses it increases circulating levels of factor VIII and von Willebrand factor.

Desmopressin is currently available in Australia in various presentations (IM/IV injection, oral tablet, sublingual wafer/melt) for several indications:

- Treatment of patients with diabetes insipidus who have a deficiency of endogenous vasopressin (100 to 1,200 µg per day, divided into 2 or 3 doses).
- Measurement of the kidney's ability to concentrate urine (that is, renal concentration capacity testing [RCCT]) or patients with suspected renal disease (single dose of 600 µg).
- Treatment of children and young adults with primary nocturnal enuresis (200 to 600 µg at bedtime).
- To prevent bleeding in patients with haemophilia A or type 1 von Willebrand's Disease (SC injection or a higher dose of nasal spray).

In Australian clinical practice, the treatment of choice for children with primary nocturnal enuresis is the pad and bell alarm. Desmopressin is used mainly to avoid problems in short term (for example, camps and sleep overs).

The Australian PIs for Minirin tablets and melt state that: "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."

Presentation/formulation

Nocdurna is an orally disintegrating sublingual tablet (ODST) or "melt" (also called oral lyophilisate), which dissolves immediately, without the need for water. A possible advantage of the ODST is enhanced compliance in elderly patients who may have difficulty swallowing conventional oral tablets.

All the excipients used in desmopressin ODST are in widespread use in the pharmaceutical industry; and at the concentrations used, are considered safe for oral use in humans.

Study CS030 compared AUC for urine osmolality for the 60 µg ODST and the 100 µg tablet in 60 over hydrated, healthy men and women. The geometric mean ratio was 0.94 (95% confidence interval (CI): 0.08, 1.11). The sponsor states that this study establishes bioequivalence between the 60 µg ODST and the 100 µg tablet.

Nocturia

The standard definition of nocturia is waking up 1 or more times per night to void, where each voiding episode is preceded and followed by sleep. Treatment is not usually initiated until 2 or more voids per night, as this is where bother is increased. Two or more voids per night was the criterion used to select patients for entry into the pivotal trials for Nocdurna.

Nocturia is a symptom complex associated with several underlying causes and pathologies; it is common in the elderly (occurring in perhaps up to 50% of men and women older than 75 years); and it is one of the most common reasons for sleep disruption (other causes: physical pain, heartburn, sleep apnoea, anxiety and depression). Waking up at night to void is said to be associated with a decrease in the quality of night time sleep, followed by day time fatigue/sleepiness, an increased risk of mood disorders, and an increased risk of falls and fractures.

Adult nocturia is a different condition from primary nocturnal enuresis seen in children and young adults.

Nocturia is associated with a variety of clinical syndromes and disorders (that is, a symptom complex, as above). Broadly speaking, it can result from:

- disorders that cause frequent low volume voids (for example, overactive bladder, bladder outlet obstruction, stiffer/less compliant/functionally smaller bladder associated with aging) or
- frequent high volume voids (for example, nocturnal polyuria, global polyuria [diabetes insipidus or mellitus]) or
- a combination of both (this is common).

Patients with sleep disorders (sleep apnoea, restless leg syndrome, anxiety and etcetera) also complain of nocturia. It is often unclear whether these patients wake up because of a true need to void or because of an unrecognised sleep disturbance, which is falsely attributed to a need to void.

As in the dot points above, nocturnal polyuria is a subset of nocturia defined as excessive volume of urine produced at night. The human body typically produces less urine while asleep. People with nocturnal polyuria produce larger volumes of urine when asleep, causing them to awaken multiple times in the night to void.

The diagnosis nocturnal polyuria is age dependent:

- < 35 years: nocturnal urine volume exceeds 20% of total 24 hour volume
- 65 + years: nocturnal urine volume exceeds 33% of total 24 hour volume.

Nocturnal polyuria has been attributed to:

- Abnormalities in diurnal variation in vasopressin secretion
- Abnormalities in the diuresis of solutes (for example, urea, sodium, potassium)
- Night time mobilisation of oedematous fluid in conditions such as congestive heart failure, nephrotic syndrome, or venous insufficiency.

However, as noted above, often patients have more than one problem presenting as nocturia (or nocturnal polyuria); for example, high volume of urine at night in combination with low volume bladder (perhaps associated with ageing) and bladder outlet obstruction.

That is, the situation is complicated because patients can have nocturnal polyuria overlaid on problems associated with frequent, low volume voids. These problems include:

- Stiffer/less compliant bladder associated with aging
- Overactive bladder (OAB)
- Benign prostatic hypertrophy (BPH)
- Hypotonic bladder
- Various neurological conditions
- Post-menopausal changes in women
- Pelvic organ prolapse in women.

Hyponatraemia

Hyponatraemia is the most important safety concern associated with desmopressin. It primarily manifests as neurological symptoms secondary to cerebral oedema.¹³ Symptoms are related to the degree of severity and the rate at which the sodium concentration changes (acute versus chronic). It is a potentially life-threatening condition.

Table 3: Classification of hyponatraemia

Severity	Sodium levels
Normal	135 to 145 mmol/L
Mild	130 to 134 mmol/L
Moderate	126 to 130 mmol/L
Severe	≤ 125 mmol/L

The first clinical manifestations of acute hyponatremia include nausea and malaise. Very severe hyponatremia (< 120mmol/L) can lead to seizures, coma and respiratory arrest.¹³

The clinical manifestations of chronic hyponatremia tend to be less severe than those of acute hyponatremia due to cerebral adaptation, which can occur over several days. Due to this adaptation process, some patients can remain asymptomatic despite sodium levels of < 120 mmol/L. Symptoms that may occur include fatigue, nausea, gait disturbance, confusion and forgetfulness.¹³ Of note, even mild, chronic hyponatremia can lead to cognitive impairment, falls and fractures.¹⁴ The increased rate of fractures is thought to be related not only to the increase risk of falls but also due to a direct impact on either bone mineral density or bone quality, although this is yet to be definitely proven.¹⁴

Older patients are at greater risk of hyponatremia due to declining physiological processes and the frequent presence of multiple co-morbidities and concomitant medications.¹⁴

Hyponatraemia is a common disorder amongst older patients (65 + years); estimated to be about 5% in an outpatient setting and up to 20% in a hospital setting.¹⁵ This is particularly important in the context of the application of Nocdurna, given that nocturnal polyuria is also more common in people as they age.

¹³ Sterns R "Manifestations of hyponatremia and hypernatremia in adults" in UpToDate, Post TW (ed), US. (Accessed 11 April 2016).

¹⁴ Soiza R L, et al Hyponatremia: Special Considerations in Older Patients. *J Clin Med* 2014, 3, 944-958.

¹⁵ Michelis M. Chapter 16, Geriatric Nephrology – online curricula of the American Society Nephrology available at <https://www.asn-online.org/education/distancelearning/curricula/geriatrics/Chapter16.pdf>

Contents of the clinical dossier

The evaluator based his evaluation on overseas reports.

The evaluator states that the sponsor provided the following:

- Day 70 preliminary assessment reports (PAR) from EU; Sweden is the reference member state (RMS); the evaluation was still in progress at the time of the clinical overview.
- Health Canada evaluation report (2012: initially registered, based on CS29/CS31 (women: 25 µg, men: 100 µg). 2013: change to dosing for men from 100 µg to 50 µg, based on CS41.)

The USA Food and Drug Administration (FDA) briefing papers from January 2015 were publicly available.¹⁶

The sponsor advised the TGA that the dossier submitted in Australia is essentially the same as that submitted in EU (reference member state [RMS]: Sweden). The pivotal/confirmatory trials are the same as those that went to the FDA's Endocrinologic and Metabolic Drug Advisory Committee (EMDAC) in January 2015; and, as above, Nocdurna was initially registered in Canada based on CS29/CS31; with a subsequent dose change for men, based on CS41 (these studies were in the Australian dossier).

This means that the evidence submitted in the Australian dossier has been thoroughly evaluated by trusted major regulators (FDA, Health Canada and Sweden's Medicines Regulator). Consequently, to avoid needless and unhelpful duplication, this Australian clinical evaluation report builds on the overseas reports; either provided by the sponsor (Canada, EU) or in the public domain (US). However, this remains very much an independent Australian evaluation.

Pharmacokinetics

Pharmacokinetic and pharmacodynamic clinical pharmacology

The clinical pharmacology of desmopressin is well characterised. Brief details relevant to this submission are given below.

Study CS30 showed that desmopressin 100 µg oral tablet formulation was bioequivalent to 60 µg of the ODS for urine osmolality and urine production.

Study CS36¹⁷ investigated low doses of Nocdurna in water loaded Japanese nocturia patients, aged 55 to 74. The doses were: 10, 25, 50, and 100 µg. The antidiuretic effect was seen at 15 to 30 minutes after administration of Nocdurna, reached a maximum effect (defined as the time urine osmolality was > 200 mOsm/kg in water loaded participants) after 60 to 120 minutes, and had an average duration of diuretic action of 3 to 5 hours.

That is, Nocdurna doses of 25 µg (women) and 50 µg (men) have a mean duration of antidiuretic effect in the range of 3 to 5 hours. This is shorter than the duration of diuretic effect of 7 to 11 hours for higher doses of 100 to 400 µg for the tablets in primary nocturnal enuresis in children.

¹⁶ <http://www.fda.gov/AdvisoryCommittees/ucm426272.htm>

¹⁷ Yamaguchi, O et al Gender difference in efficacy and dose response in Japanese Patients with nocturia treated with four different doses of desmopressin orally disintegrating tablet in a randomized Placebo controlled trial. *BJU Int.* 2013; 111: 474-484

Study CS29 confirmed the sex difference in the pharmacodynamic (PD) effect of desmopressin on nocturnal urine volume. In women, desmopressin had a lower ED₅₀ (dose giving 50% of maximal effect) in the ability to decrease the average nocturnal urine volume than in men. For women, the minimal effect dose was 25 µg, with adverse events increasing with higher doses. Additional pharmacokinetic (PK)/PD modelling found that the weight corrected concentration at 50% of the maximal effect (EC₅₀) for decrease in urine volume was 2.7 (95% CI: 1.3, 8.1) times higher in men than women.

That is, women are more sensitive to desmopressin than men. However, it is unclear whether this is simply because women have a smaller body size than men.¹⁸

Hepatic impairment

There is limited experience in patients with hepatic impairment. Routine pharmacovigilance of other medicines containing desmopressin has not identified any major safety concerns.

The proposed PI states, “No studies have been performed in this population.”

Renal impairment

Desmopressin is mainly eliminated by enzymatic degradation in the circulation and excreted renally in the urine. The terminal half-life in patients with renal impairment is increased and this could increase the duration-of-action, which could increase the risk of hyponatraemia.

The proposed PI states: “Depending on the degree of renal impairment the AUC and half-life are increased with the severity of the renal impairment. Desmopressin is contraindicated in patients with moderate and severe renal impairment (creatinine clearance below 50 mL/min).” The sponsor should amend the PI to refer to estimated glomerular filtration rate (eGFR) not creatinine clearance (CrCl). Given the modest efficacy of Nocdurna, it could be argued that any degree of renal impairment would mean that use should be contraindicated. Further, efficacy could be compromised with impaired kidney function.

Dosage selection for the pivotal studies

In the Australian dossier, the sponsor stated that the Nocdurna program commenced with the 28 day dose finding study CS29 (placebo versus 1 of 4 doses of desmopressin: 10, 25, 50, and 100 µg). CS31 was the open label extension study of CS29.

The sponsor then stated that, based on the results of CS29/CS31, two confirmatory studies were conducted:

- CS40 in women testing the 25 µg dose.
- CS41 in men testing the 50 µg and 75 µg doses.

¹⁸ Clarification: Gender differences in drug exposure when single melt doses between 60 and 240 µg were administered orally were not statistically significant when adjusted for body weight, thus the observed differences in PD response between men and women are unlikely to be explained by PK differences. Juul K V et al Gender difference in antidiuretic response to desmopressin *Am J Physiol Renal Physiol* 2011; 300: 1116–1122,

Efficacy

Studies providing efficacy data

Table 4: Clinical trials

Trial	Design	Intervention	n	Duration	Co-primary endpoints
CS29	Randomised Parallel group	10, 25, 50, 100 mcg	799	4 weeks	Change in number of nocturnal voids.
CS40	Placebo controlled	25 mcg	268 women only	12 weeks	Responder: >33% reduction in number of nocturnal voids.
CS41		50, 75 mcg	395 men only	12 weeks	

For the full details of the evaluation of clinical efficacy please see Attachment 2.

Safety

Studies providing safety data

Safety data was evaluated from the following studies

- CS40
- CS41

For the full evaluation of the safety aspects of this submission please see Attachment 2.

Evaluator's conclusions on safety

Hyponatraemia is the most important safety concern, which is based on the known mechanism of action (that is, water retention).

Thrombosis is a potential risk, based on desmopressin's haematological effects (for example, it has a registered indication for von Willibrand's disease). However, the dose used for von Willibrand's disease is much higher than the doses proposed for nocturnal polyuria. There was no signal for thromboembolic events in the Studies CS40/CS41; although these trials were only of three months duration. Thrombosis is listed as an important potential risk in the summary of safety concerns; routine pharmacovigilance (spontaneous reporting) is proposed.

First round benefit-risk assessment

First round assessment of benefits

The results for the co-primary endpoints from CS40/CS41 were statistically significant; however, it is uncertain whether the results were clinically significant. More specifically, the average benefits of Nocdurna, based on CS40/CS41, were for women treated with 25 µg a: reduction of one night time void per 4 to 5 days; and in men treated with 50 µg a reduction of one night time void per 2 to 3 days.

The other co-primary endpoint was a 33% reduction in night time voids at 3 months. The average baseline number of voids in CS40/CS41 was 3 voids per night. Consequently, for the typical/average patient in CS40/CS41, a 33% reduction in night time voids was a decrease from 3 to 2 voids per night; the evaluator was uncertain whether such a decrease

is clinically significant. It was noted that one quarter of women and one third of men did not achieve this improvement.

Various secondary endpoints in CS40/CS41 including: time to first nocturnal void, mean nocturnal void volume and nocturia quality of life questionnaire (N-QoL) were generally supportive of a small treatment effect. In CS41 (men), the placebo subtracted time to first nocturnal void was 39 minutes longer with Nocdurna; and the placebo subtracted mean nocturnal urine volume was 78 mL less.

The evaluator was uncertain whether efficacy has been satisfactorily established within the pivotal trials.

Nocdurna was less effective when the nocturia is due a combination of nocturnal polyuria overlaid with frequent low volume voids. CS40/CS41 excluded patients with severe daytime voiding dysfunction, however, in the real world of everyday clinical practice, patients with severe (however defined) daytime voiding dysfunction might be prescribed Nocdurna. If this were to occur, the average benefit to the population of patients using Nocdurna, post-marketing, might be even more uncertain than in the pre-market studies (CS40/CS41).

The proposed Australian indications are for nocturnal polyuria that *has not responded to lifestyle and behavioural modifications* (before bedtime drink only enough to satisfy thirst; avoid alcohol and caffeine containing beverages). Given the response in the placebo arm of the pivotal trials, there is the concern that lifestyle factors may have been inadequately studied. Lifestyle interventions do not carry the same potential harm (that is, hyponatraemia) as Nocdurna.

First round assessment of risks

The most important harm is the risk of hyponatraemia. Other adverse effects/reactions include dry mouth, headache and nausea, which do not carry the same risk to health as hyponatraemia.

The elderly are at greater risk of hyponatraemia because of declining physiological reserve and the frequent presence of comorbidities and concomitant medications. Prevalence estimates are: outpatients 5%, inpatients 20%.¹⁹

The clinical studies CS40/CS41 included a number of inclusion/exclusion criteria and monitoring to minimise the risks of hyponatremia. These included the following:

- Excluded patients at risk of hyponatremia such as those with syndrome of inappropriate antidiuretic hormone secretion (SIADH), cardiac failure and hyponatremia (serum sodium < 135 mmol/L) at screening
- Prohibited initiation, during the trial, of specific medicines that may cause hyponatraemia (that is, TCADs, selective serotonin reuptake inhibitors (SSRIs), non-steroidal anti-inflammatory drugs (NSAIDs), chlorpropamide, diuretics, carbamazepine, and etcetera). Patients who were already on the specific medications had to have been on a stable dose for 3 months prior to the screening date
- Excluded patients on loop diuretics
- Instructed patients to limit fluid intake 1 hour before study drug and until 8 hours after study drug

¹⁹ Michelis M. Chapter 16, Geriatric Nephrology – online curricula of the American Society Nephrology available at <https://www.asn-online.org/education/distancelearning/curricula/geriatrics/Chapter16.pdf>

- Stopped treatment if an acute illness occurred that could result in fluid and/or electrolyte imbalances
- Withdrew patients if serum sodium was ≤ 125 mmol/L
- Measured serum sodium at baseline, twice within Week 1, and then monthly in CS40, with additional measurements in CS41 at Week 2 and 3 in Part I and weekly measurements in Part II.

The clinical evaluator was concerned how similar selection criteria and monitoring could occur in the real world of everyday clinical practice.

The clinical evaluator was concerned that with longer term use of desmopressin in the real world of everyday clinical practice and the likely use of concomitant medicines the risk of hyponatraemia will be higher than that reported for CS40/CS41.

Clinical questions and second round evaluation of clinical data submitted in response to questions

For details of the clinical questions, the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Nocturia is an important problem that can materially reduce patients' quality of life.

The results for the co-primary endpoints were statistically significant. Also, the results for the secondary endpoints (including N-QoL) provide some support for the co-primary endpoints.

However, the average benefits of Nocdurna were modest: women (25 µg): reduction of one night time void per 4 to 5 days; men (50 µg): reduction of one night time void per 2 to 3 days.

One important concern is the risk of hyponatraemia in the real world of everyday clinical practice in Australia.

There is therefore uncertainty about whether the benefit-risk balance is favourable. Two overseas regulatory agencies (Health Canada, Swedish NRA and CMS) have decided that the benefit-risk balance is favourable; whereas the FDA have decided it is not, based on the currently available data.

- Health Canada has stated: With all recommendations and measures to be taken prior or during treatment to avoid the development hyponatremia [that is, baseline serum measures for all patients and repeat measures in Week 1 and Month 1], it can be concluded that the benefit of desmopressin in the treatment of the proposed indication outweighs its risk.
- The Swedish NRA evaluation has stated: With adequate monitoring the risk of hyponatraemia is considered possible to manage.
- The FDA stated that "... while some of these changes might be helpful in minimising the risk of hyponatraemia, and thereby improving the benefit-risk calculus, the FDA is still seeking clarity on the clinical benefit." The sponsor is in discussion with the FDA about potentially conducting further studies.

The most recent report of the Australian Commission on Safety and Quality in Health Care on medication safety (2013) stated that 12% of medical admissions (that is, 230,000

admissions per year) were attributable to adverse reactions associated with medications; a (conservative) estimate of cost was \$1.2B per year. There is concern and uncertainty around whether Nocdurna might contribute to this problem, via the well-known adverse reaction of hyponatraemia. This might be particularly the case when Nocdurna is used long term for a chronic condition, in every day clinical practice (that is, outside of the context of a closely monitored, 3 month clinical trial, which had carefully selected trial participants). There is also uncertainty as to whether the benefits of Nocdurna are sufficient to offset the risks associated with hyponatraemia.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) EU-RMP version 1 dated 23 March 2015 (data lock point 31 December 2014) and the Australian Specific Annex (ASA) dated 22 October 2015 to the EU-RMP; updated EU-RMP version 3.0 dated 23 February 2016 (data lock point 30 November 2015) and the ASA version 2.0 dated 17 June 2016 which were reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 5.

Table 5: Summary of ongoing safety concerns

Summary of safety concerns	
Important identified risks	Hyponatraemia
Important Potential risks	Thrombosis Anaphylactic reaction (including allergic reactions due to fish gelatine in melt formulation)
Missing information	None

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for all the safety concerns.²⁰ No additional pharmacovigilance has been proposed.

Risk minimisation activities

The sponsor states in the ASA: 'Risk minimisation activities beyond routine risk minimisation are not required for Nocdurna.'²¹

²⁰ Routine pharmacovigilance practices involve the following activities:

All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; Reporting to regulatory authorities; Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling; Submission of PSURs; Meeting other local regulatory agency requirements.

Reconciliation of issues outlined in the RMP report

Table 6 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised and the evaluation of the sponsor's responses.

Table 6: Reconciliation of issues in the round 1 RMP evaluation report

Reconciliation of issues in the round 1 RMP evaluation report
<p>TGA recommendation 1: Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request for information. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>
<p>Sponsor's response: Ferring acknowledges this and has provided safety information that is relevant and necessary through the updated ASA and the updated version of the RMP (version 3.0).</p>
<p>RMP evaluator comment: The sponsor's response is satisfactory. The evaluator has noted the updated EU-RMP and ASA.</p>
<p>TGA recommendation 2: The proposed indication does not include the full definition of nocturnal polyuria. According to 'Nocturia; a guide to assessment and management' published by the RACGP²² diagnosis of nocturnal polyuria needs to be based on the number of voids and the volume; '> 20% of 24 hour urine volume in young adults, > 33% in older adults'. Without assessing the volume, patients with bladder storage disorders could be inappropriately treated and exposed to unnecessary risks of adverse events. Therefore, the Delegate's attention is drawn to the lack of adequate definition of nocturnal polyuria in the proposed indication.</p>
<p>Sponsor's response: The definition of nocturia listed below has now been included in the PI under Dosage and Administration. This definition is currently in the Minirin Melt Company Core Data Sheet and is in agreement with the International Continence Society (ICS) definition.</p> <p>Nocturnal polyuria exists if 33% or more of a patient's daily urine output is produced at night. It can be suspected by excluding other causes of nocturia. However, its presence can be determined by dividing the nocturnal urine volume by the 24 hour urine volume.</p>
<p>RMP evaluator comment: The evaluator has noted the sponsor's response. The adequacy of the PI is to be determined by the Delegate. The evaluator has noted that the approved indication in the UK is restricted to idiopathic nocturnal polyuria:</p>

²¹ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

²² RACGP = Royal Australian College of General Practitioners

<http://www.racgp.org.au/afp/2012/june/nocturia-a-guide-to-assessment-and-management>

Reconciliation of issues in the round 1 RMP evaluation report

'Noqdirna is indicated for symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults'.²³

TGA recommendation 3: It is noted that the sponsor plans to upgrade 'anaphylactic reaction' from an 'important potential risk' to an 'important identified risk' in the next RMP update. The sponsor should provide rationale for this planned action, relevant information, such as the number of post authorisation anaphylactic reaction reports should be included.

Sponsor's response: The upgrade of 'anaphylactic reaction' from an 'important potential risk' to an 'important identified risk' was introduced in alignment with the recommendations from the European periodic safety update report (PSUR) assessment in 2015.²⁴ Relevant information, such as the number of post-authorisation case reports of anaphylactic reactions or symptoms, suggestive of severe allergic reactions, are included in the RMP version 3.0.

RMP evaluator comment: The sponsor's response is satisfactory. The evaluator has noted the following statement in the updated EU-RMP:

Post-marketing surveillance:

A search using the relevant standardised MedDRA queries (SMQs) (MedDRA terms) resulted in 87 serious case reports of anaphylactic reactions or symptoms suggestive of severe allergic reactions.

The majority of the cases were reported with solution for injection (38 %), followed by nasal drops solution (26 %), tablet (16 %), oral lyophilisate (11 %) and nasal spray (2%). In 7% of the cases the formulation was unknown. It is not possible to estimate the frequency based on post-marketing data, however it is considered to be a very rare undesirable effect.

'Hypersensitivity to the active substances or to any of the excipients listed in the 'Description section' has been listed as a contraindication. This is acceptable routine risk minimisation.

TGA recommendation 4: Subject to the evaluation outcomes of the nonclinical and clinical aspects of the safety specification, it is noted that the following safety concerns have been identified with other desmopressin formulations. The sponsor should provide justification to why they are not relevant to the use of Nocdurna in adult patients, or add them to the ASA:

- a. Water intoxication
- b. Seizures
- c. Headache
- d. Polypharmacy drug interactions.

Sponsor's response: Water intoxication and seizures are consequences of severe hyponatraemia and/or inappropriate correction of hyponatraemia. As Ferring

²³ <http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1467955220804.pdf>

²⁴ PSUSA/00000964/201412, EMA/PRAC/589834/2015

Reconciliation of issues in the round 1 RMP evaluation report

already monitors all reports of hyponatremia and associated events, including headache, water intoxication and seizures, these events/safety concerns are implicitly monitored. Additionally, hyponatraemia has a SMQ. SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports and the included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etcetera. As the SMQ Hyponatraemia/SIADH includes headache, water intoxication and seizures, the events/safety concerns are therefore part of the data analysis of the identified risk 'Hyponatraemia due to water retention, which could be caused also by overdose'.

Regarding polypharmacy drug interactions, the PI for desmopressin notes that it is unlikely that desmopressin will interact with drugs affecting hepatic metabolism, since desmopressin has been shown not to undergo significant metabolism. Therefore the interactions with drugs that may be of interest are those medicines that may induce water retention/hyponatraemia. Presently this risk is already captured by the identified risk of hyponatraemia.

Thus Ferring is of the view that these events listed by the evaluator already fall under the important identified risk of "Hyponatraemia due to water retention, which could be caused also by overdose", and therefore, disagrees these events should be listed as separate safety concerns.

RMP evaluator comment: The sponsor's response is acceptable.

TGA recommendation 5: The clinical consequence of hyponatraemia differs among patients as some patients are at a higher risk and are more sensitive to electrolyte imbalance. It is recommended that 'use in patients who are more sensitive to hyponatraemia, including the elderly' is listed as a separate potential risk.

Sponsor's response: Ferring has included the important identified risk "Hyponatraemia in elderly patients (≥ 65 years)", specifically for Nocdurna and this has been added as an important identified risk in the enclosed RMP version 3.0.

RMP evaluator comment: The sponsor's response is acceptable.

TGA recommendation 6: The evaluator has noted the sponsor's discussion on off-label use in the EU-RMP. The possibility of off-label use in patients with other conditions, such as congestive heart failure, and bladder storage disorders, could not be dismissed. Off-label use of desmopressin expose patients to risks associated with the product, and more importantly, mask the symptoms of the underlying problems that should be attended. Therefore, it is recommended that off-label use is added as a potential risk in the ASA.

Sponsor's response: "Precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency" is added as an important potential risk, specifically for Nocdurna, in RMP version 3.0.

Having congestive heart failure and bladder storage disorders addressed in sections Contraindications and Precautions is considered sufficient to inform the HCPs and prevent from using Nocdurna in patients with these disorders.

Reconciliation of issues in the round 1 RMP evaluation report

In the enclosed version 3.0 of the RMP (approved within the EU DCP), "Precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency" is already included as an important potential risk. This risk will be also addressed in the planned Category 3 post-authorisation safety study (PASS) in EU: the collected data will help to describe the risk of precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency in association with Nocdurna treatment when prescribed according to approved SmPC.

RMP evaluator comment: The evaluator has noted the updated content in the EU-RMP and the draft PI. The sponsor's response is acceptable.

TGA recommendation 7: As the sponsor advises in the EU-RMP, there is limited clinical experience in using desmopressin in the following patient groups. They should be added as missing information:

- a. Use in pregnancy
- b. Use in patients with hepatic impairment.

Sponsor's response:

- a. Ferring has added "Use in pregnancy" as missing information in the latest submitted version of the RMP (version 3.0) in alignment with the recommendations from the European PSUR assessment in 2015.²⁴
- b. Ferring does not consider "use in patients with hepatic impairment" to be missing information as in vitro human liver microsome metabolism studies of desmopressin conducted have shown no significant amount metabolised in the liver by the cytochrome P450 system. Therefore, human liver metabolism in vivo by the cytochrome P450 system is unlikely to occur. Also the effect of desmopressin on the pharmacokinetics of other drugs is likely to be minimal due to its lack of inhibition of the cytochrome P450 drug metabolising system.

Furthermore, since 1972, desmopressin has been marketed worldwide in several populations, including intranasal, intravenous/subcutaneous, and oral formulations for the treatment of diabetes insipidus and primary nocturnal enuresis. These formulations are available at much higher doses than Nocdurna. Thus to date, there have been no post-market safety signals detected that have altered the risk benefit profile as described in the current PIs for desmopressin.

RMP evaluator comment: The sponsor's response is acceptable.

TGA recommendation 8: The limited experience in the elderly, especially long term safety, has been identified during the evaluation of the clinical data in the clinical evaluation report. This should be added as missing information in the ASA.

Sponsor's response: "Long term use in elderly patients" specifically for Nocdurna, is added as missing information in the enclosed RMP version 3.0.

RMP evaluator comment: The sponsor's response is acceptable.

Reconciliation of issues in the round 1 RMP evaluation report

TGA recommendation 9: The sponsor has stated that the safety profile of desmopressin is well established during its 40 years' of clinical use. However, the safety profile of its use in the proposed indication has not been well characterised. Therefore, the sponsor should develop a plan of additional pharmacovigilance to further characterise the safety profile in the target population of the proposed indication.

Sponsor's response: This is addressed in the enclosed RMP version 3.0.

RMP evaluator comment: The sponsor's response has not clearly stated its intention. The evaluator has noted that according to the updated EU-RMP, a Category 3 PASS has been planned with protocol in development. The sponsor states in the updated ASA under '2.4 Studies referenced in the pharmacovigilance plan of the RMP': 'Not applicable as no clinical program has been conducted for desmopressin and no post-authorisation efficacy studies have been planned or conducted in Australia'.

The sponsor should revise the ASA as follows:

The PASS study should be added in the ASA under section 2.4.

The sponsor should clarify whether the PASS study will include Australian patients. If Australia is not to be included in the study, the sponsor should provide its justification to why it considers the study results are applicable for Australia, or to provide an alternative plan of local additional pharmacovigilance activities.

In addition, the sponsor should provide the study protocol for review by the TGA when it becomes available.

TGA recommendation 10: In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the following advice is added to the draft PI:

Before treatment, causes of nocturia should be assessed, including other medical conditions and other medications. The underlying causes of nocturia should be managed before Nocdurna treatment is started.

Sponsor's response: Ferring have included an additional precaution statement to address this point. The new precaution statement is listed below:

Under Precautions:

Before treatment with Nocdurna is considered, the underlying cause(s) of nocturia in a patient should be investigated. Nocdurna treatment should only be considered when nocturnal polyuria has been established as the primary cause of nocturia. However, patients, in particular the elderly, should undergo clinical examination and questioning before commencing treatment with Nocdurna, given that nocturnal polyuria can be a symptom of cardiovascular or other medical conditions associated with fluid overload. If there is any suspicion of such coexistent conditions, treatment with Nocdurna is not recommended (see Contraindications). Also, lifestyle modifications which may contribute to nocturia should be considered before Nocdurna treatment and where appropriate initiated (for example before bedtime drink only enough to satisfy thirst; and avoid alcohol and caffeine containing

Reconciliation of issues in the round 1 RMP evaluation report

beverages).

RMP evaluator comment: The sponsor's response is acceptable from the RMP perspective. The sponsor's proposed PI change is for the Delegate's consideration.

Summary of recommendations

Key changes to the updated RMP.

In their response to the TGA consolidated request for information the sponsor provided an updated RMP (version, date). Key changes from the version evaluated at Round 1 are summarised in Table 7.

Table 7: Key changes to the updated RMP

Key changes to the updated RMP	
Safety specification	<p>The summary of safety concerns has been split into two tables:</p> <p>Summary of safety concerns Ferring desmopressin products:</p> <ul style="list-style-type: none"> • Important identified risks: Hyponatraemia due to water retention, which could be caused also by overdose; allergic reactions and hypersensitivity, including anaphylactic reaction; • Important potential risks: Thrombotic events; • Missing information: Limited data on pregnancy (newly added). <p>Summary of safety concerns specifically for Nocdurna:</p> <ul style="list-style-type: none"> • Important identified risks: Hyponatraemia in elderly patients (≥ 65 years) (newly added); • Important potential risks: Precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency (newly added); • Missing information: Long-term use in elderly patients (newly added).
Pharmacovigilance activities	<p>A Category 3 PASS has been added in the EU-RMP to monitor the following risks:</p> <ul style="list-style-type: none"> • Important identified risk: Hyponatraemia in elderly patients ≥ 65 years; • Important potential risks: Precipitation of overt congestive cardiac failure; new occurrence or worsening of existing cardiovascular events; thromboembolic events; • Missing information: long term use in elderly patients.

Key changes to the updated RMP

Risk minimisation activities

Routine risk minimisation has been added for the newly added safety concerns.

Suggested wording for conditions of registration

RMP

As there are outstanding RMP issues to be addressed, no suggested wording for conditions of registration could be provided at this stage.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

Desmopressin is a synthetic analogue of arginine vasopressin (AVP), a natural pituitary hormone responsible for regulating water retention and serum concentration of sodium. At high plasma concentrations, desmopressin also increases circulating levels of coagulation factor VIII and von Willebrand Factor, but has little, if any, pressor activity (however this is not relevant to the small doses proposed).

The EC₅₀ (half maximal effective concentration; potency) of desmopressin is estimated to be < 2 pg/mL, and maximal effect (E_{max}) is 4 to 5 pg/mL. The therapeutic levels achieved with exogenous desmopressin are in excess of this. The most important safety concern associated with the use of desmopressin is hyponatraemia. Desmopressin allows for, rather than induces, hyponatraemia since it acts on the kidneys to stimulate continued water conservation.

Desmopressin is currently available in Australia in various presentations (IM/IV injection, oral tablet, sublingual wafer/melt) for several indications (as shown in Table 1 above):

- Treatment of patients with diabetes insipidus who have a deficiency of endogenous vasopressin (100 to 1,200 µg per day, divided into 2 or 3 doses).
- Measurement of the kidney's ability to concentrate urine (that is, renal concentration capacity testing [RCCT]) or patients with suspected renal disease (single dose of 600 µg).
- Treatment of children and young adults with primary nocturnal enuresis (200 to 600 µg at bedtime).
- To prevent bleeding in patients with haemophilia A or type 1 von Willebrand's Disease (s/c injection or a higher dose of nasal spray).

Thus, the dose proposed is much lower than that for the other indications

Overseas regulatory status

Canada

- An initial application was submitted to Health Canada in December 2011 and registered in December 2012. This registration was based on CS29 and its long-term extension study CS31. Indication:

Nocdurna is indicated for the treatment of nocturia in adults with four or less nocturnal voids. An insufficient number of adults with more than four nocturnal voids were studied to allow a conclusion on the efficacy of Nocdurna in these subjects.

EU

The application was made in April 2015 via a decentralised procedure (DCP). The reference member state (RMS) is Sweden. Based on the interim evaluation reports, the application was considered 'approvable'.

FDA

Studies CS29 and CS31 were submitted to the FDA in 2009. The FDA was concerned that the benefits of reduced frequency of nocturnal voids may not be outweighed by the harms of hyponatremia. The FDA recommended a longer term study with lower doses. These studies (CS40 and CS41) were submitted in 2012. In January 2015, the FDA Endocrine and Metabolic Advisory Committee voted 10 to 5 with 2 abstentions to recommend the FDA not approve the medicine.

Regulatory action for the risk of hyponatraemia associated with desmopressin

United States

In 2007 the FDA issued an alert requesting all desmopressin manufacturers remove the indication for primary nocturnal enuresis for the nasal formulations. The FDA also requested an update to the PIs to include information about severe hyponatraemia and seizures.

EU

In 2006 the EMA's Pharmacovigilance Working Party recommended withdrawal of the indication for primary nocturnal enuresis for the nasal formulations. They also recommended the addition of a warning about the possible risk of severe hyponatraemia when the nasal spray is used in patients with central diabetes insipidus.

UK

In 2008 the MHRA added a black triangle to the desmopressin melt products to expedite all reports of hyponatraemia or associated prodromal symptoms. The black triangle was removed in 2011.

Quality

The quality evaluator did not have any objections to the registration of Nocdurna.

The drug substance is identical from a chemistry, manufacturing, quality control and stability perspective to that previously approved for Minirin tablets 200 µg (AUST R 93731) and Minirin MeltT wafers containing 60 µg, 120 µg and 240 µg (AUST Rs 121720, 121721, and 121722).

Nonclinical

The nonclinical evaluator did not have any concerns about the registration of Nocdurna.

Clinical

The condition for which treatment is proposed:

The standard definition of nocturia is waking up 2 or more times per night to void, where each episode is preceded and followed by sleep. The standard definition of nocturia is waking up 1 or more times per night to void, where each voiding episode is preceded and followed by sleep. Treatment is not usually initiated until 2 or more voids per night, as this is where bother is increased.

Nocturia is a symptom complex associated with several underlying causes and pathologies. It occurs in 50% of men and women older than 75 years old. It is reported to be one of the most common reasons of sleep disruption. Waking at night to void is associated with a decrease in the quality of night time sleep, day time fatigue/sleepiness, increased risk of mood disorders and increased risk of falls.

Causes of nocturia include:

- disorders of frequent low volume voids for example, overactive bladder, bladder outlet obstruction, stiffer/less compliant functionally smaller bladder associated with aging
- frequent high volume voids that is polyuria for example diabetes insipidus (DI), diabetes mellitus (DM)
- redistribution of excessive fluid associated with heart failure, postural hypotension, venous insufficiency
- sleep disorders

Nocturnal polyuria is present when an increased proportion of the 24 hour urine output occurs at night. It is thought to contribute to approximately 75% of those with bothersome polyuria.

Pharmacology

Study CS36 investigated 10, 25, 50 and 100µg doses of Nocdurna in Japanese patients aged 55 to 74 years with nocturia who were water loaded. The anti-diuretic effect was seen at 15 to 30 minutes and reached maximal effect after 60 to 120 minutes and had an average duration of action of 3 to 5 hours.

Study CS29 confirmed the sex difference in the pharmacodynamic effect of desmopressin on nocturnal urine volume.

Bioequivalence study between the melts and tablets was done for 200, 400 and 800 µg doses in health volunteers. Desmopressin is largely destroyed in the gastrointestinal tract. Therefore, bioavailability is low (0.25%). In addition there is high intra-patient variability in pharmacokinetics. The AUC is thought to be more important than C_{max} in PD effect.

Efficacy

CS41 - men

Design

A three month, parallel group, placebo controlled double blind study. Patients advised on lifestyle changes to reduce nocturnal voiding. Used analysis of covariance (ANCOVA) for analysis.

Patients

Selected inclusion criteria

- Male and ≥ 18 years of age

- At least 2 nocturnal voids every night in a consecutive 3 day period during the screening period

Selected exclusion criteria

- Evidence of severe daytime voiding dysfunction (protocol defined criteria)
- Interstitial cystitis
- Chronic prostatitis/chronic pelvic pain syndrome
- Suspicion of bladder outlet obstruction (BOO) or urine flow < 5 mL/sec
- Surgical treatment, including transurethral resection, for BOO or benign prostatic hyperplasia (BPH) within the past 6 months
- Urinary retention or a post void residual volume in excess of 250 mL
- Habitual or psychogenic polydipsia
- Central or nephrogenic diabetes insipidus
- Syndrome of inappropriate anti-diuretic hormone
- Current or a history of urologic malignancies
- Genitourinary tract pathology
- Neurogenic detrusor activity (detrusor overactivity)
- Suspicion or evidence of cardiac failure
- Uncontrolled hypertension
- Uncontrolled diabetes mellitus
- Hyponatremia (Serum sodium level must have been within normal limits)
- Renal insufficiency (according to protocol definition)
- Hepatic and/or biliary diseases (according to protocol definition)
- History of obstructive sleep apnoea
- Previous desmopressin treatment for nocturia
- Treatment with another investigational product 3 months prior to screening
- Concomitant treatment with any prohibited medication; for example loop diuretics. Some specific medications were allowed if the subject had been on a stable dose for the 3 months prior to the screening date; alpha-blockers, 5-alpha-reductase inhibitors, antimuscarinic therapy for overactive bladder, sedative/hypnotic medications, Selective serotonin reuptake inhibitors (SSRIs), non-steroidal anti-inflammatory agents (NSAIDs), chlorpropamide, carbamazepine, amiodarone, sildenafil under strict conditions.
- Known alcohol or substance abuse

Intervention

Part I: Desmopressin 50 µg or 75 µg (double blinded) or placebo

Part II: Desmopressin 100 µg

Results

- 395 patients were randomised.

Table 8: Change in mean number of nocturnal voids (Full Analysis Set (FAS)) after 3 months

	Desmopressin	Placebo	Comparison vs placebo		
			Treatment contrast	95% CI	p-value
Adjusted means 75 µg	-1.29	-0.88	-0.41	[-0.61, -0.22]	<0.0001*
Adjusted means 50 µg	-1.25	-0.88	-0.37	[-0.57, -0.17]	0.0003*

The difference in proportion of subjects with > 33% reduction in mean number of nocturnal voids was similar with 50 and 75 dose. The risk ratio of Nocdurna 50µg compared to placebo was 1.3 (95% CI 1.1-1.5).

Of the secondary endpoints: the mean change from baseline in time to first nocturnal void was 42 minutes. No significant difference with age.

There was a significant improvement (p = 0.385) in the nocturnal quality of life score for 50 µg of Nocdurna (total score 18.37) compared with placebo (total score 13.88).

CS40 - women

Design

- 3 month, parallel group, placebo controlled double blind study. Patients advised on lifestyle changes to reduce nocturnal voiding. Used ANCOVA for analysis.

Patients

Similar to CS41.

Intervention

Desmopressin 25 µg.

Results

Total of 268 patients. 87% completed. Adverse events in 2%.

Mean age 60 years. About 50% < 65 years. Mean number of nocturnal voids 2.8.

Adjusted mean change in nocturnal voids was -1.46 for desmopressin and -1.24 for placebo. Treatment difference -0.22 (95% CI -0.42, -0.02) p = 0.028.

Probability of > 33% response was 0.76 in desmopressin and 0.64 in placebo. The risk ration for Nocdurna 25 µg was 1.2 (95% CI 1.0-1.36).

Secondary analysis stratified by age showed that only those > 65 years had a statistically significant placebo subtracted difference in change from baseline of mean nocturnal voids and proportion of subjects with > 33% reduction in mean nocturnal voids. The treatment difference for time to first void for Nocdurna 25µg compared to placebo was 49 minutes. There was a significant improvement (p = 0.0226) in the nocturnal quality of life score. The total score for the Nocdurna group was 27.24 compared to the placebo group 21.90.

CS29

Patients

For a description of the patients in this study please see Attachment 2.

Intervention

Desmopressin ODST, 10, 25, 50, 100 µg.

Comparator

Placebo.

*Endpoints**Co-primary*

- Change in mean number of nocturnal voids from baseline to final visit (Day 28)
- Proportion of patients with 33% + decrease in mean number of voids from baseline to final visit (Day 28)

Secondary

- Initial period of undisturbed sleep
- Total sleep time
- N-QoL; Nocturia Quality of Life questionnaire
- Nocturnal urinary volume.

Phases

Phase 1; 28 days

Phase 2; 6 month extension (double blind)

- Patients on active treatment continued on same treatment
- Patients on placebo were re-randomised to one of the 4 active treatment groups.

CS31 was an open label extension of Part II of CS29

Results 28 days

Results for 28 days are shown in Table 9. Note placebo effect.

Table 9: Study CS29 Results at 28 days

Nocturnal voids [□]	Placebo [¶] (n=156) [□]	10-mcg [¶] (n=155) [□]	25-mcg [¶] (n=152) [□]	50-mcg [¶] (n=148) [□]	100-mcg [¶] (n=146) [□]
Baseline (mean) [□]	3.3 [□]	3.2 [□]	3.4 [□]	3.4 [□]	3.2 [□]
Day-28 (mean) [¶]	2.4 [¶]	2.4 [¶]	2.4 [¶]	2.2 [¶]	1.8 [¶]
Diff (mean) [¶]	-0.9 [¶]	-0.8 [¶]	-1.0 [¶]	-1.2 [¶]	-1.4 [¶]
p-val versus plac [□]	[□]	0.93 [□]	0.31 [□]	0.02 [□]	<0.0001 [□]
Responders 28-day % [¶]	47% [□]	47% [¶]	50% [¶]	53% [¶]	71% [¶]
p-val versus plac [□]		0.94 [□]	0.55 [□]	0.27 [□]	<0.0001 [□]

Post hoc analysis by sex

- Women responded to lower doses with statistically significant difference to placebo for mean nocturnal voids and % responders at 25 and 50 µg dose
- Men there was only a statistically significant difference for the 100 µg dose

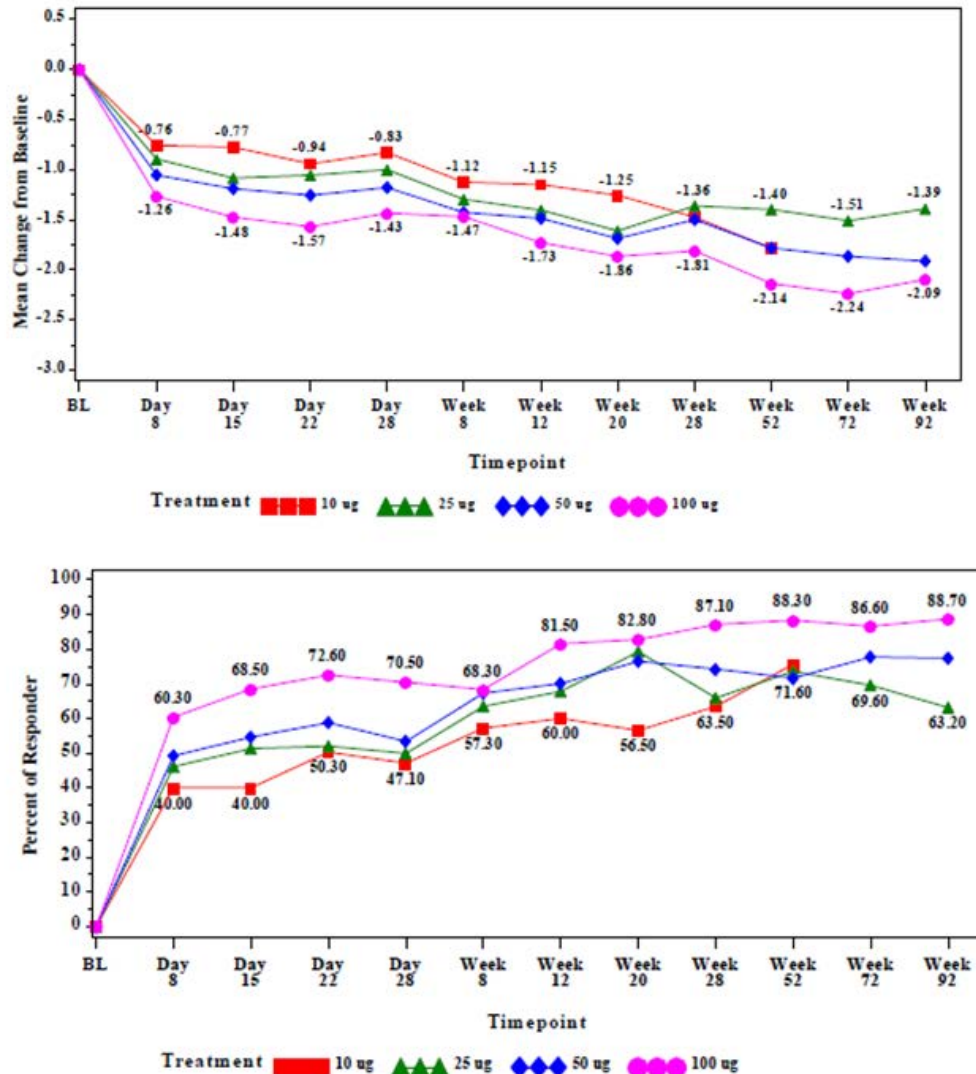
Open label extension CS31

NB those treated initially with 10 µg were randomised to bigger doses. About 50% withdrew during the duration of the study. Adverse events in around 10%

Mean age 61 years, about 50% < 65 years

There was a continuing decrease in the number of nocturnal voids over the duration of the study.

Figure 2: Durability of Effect: change from baseline in mean number of nocturnal voids and durability of effect: 33% responder status



These results need to be interpreted with caution due to the high dropout rate. Those who remained on treatment were more likely to have responded. Thus it represents evidence that in some patient's treatment may help.

Safety

Overall 1,443 subjects received at least 1 dose of the trial drug in the Phase III trials. There were 827 subjects > 65 years, the vast majority, 645 subjects (44.7%) were > 65 to 75 years old. The numbers > 75 years were 175 (12.1%) and only 7 subjects (0.5%) were older than 85 years. A total of 114 patients' \geq 65 years have been exposed to desmopressin for more than 2 years at doses ranging from 25 to 100 μ g with no relevant differences in exposure pattern between doses or by age.

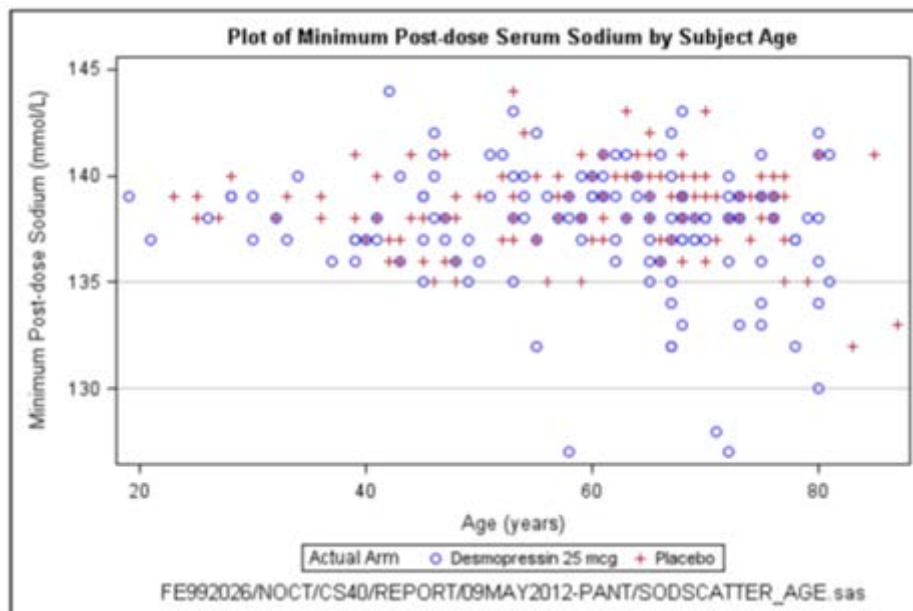
To address the risks of hyponatraemia with Nocdurna, Studies CS40/CS41:

- Excluded patients at risk of hyponatraemia such as those with syndrome of inappropriate antidiuretic hormone secretion (SIADH), cardiac failure and hyponatremia (serum sodium < 135 mmol/L) at screening.
- Prohibited initiation, during the trial, of specific medicines that may cause hyponatraemia (that is, TCADs, SSRIs, NSAIDs, chlorpropamide, diuretics, carbamazepine, etcetera). Patients who were already on the specific medications had to have been on a stable dose for 3 months prior to the screening date.
- Excluded patients on loop diuretics.
- Instructed patients to limit fluid intake 1 hour before study drug and until 8 hours after study drug.
- Stopped treatment if an acute illness occurred that could result in fluid and/or electrolyte imbalances.
- Withdrew patients if serum sodium was ≤ 125 mmol/L.
- Measured serum sodium at baseline, twice within Week 1, and then monthly in CS 40, with additional measurements in CS 41 at Week 2 and 3 in Part I and weekly measurements in Part II.

CS 40

- Similar number of adverse events (AEs) in desmopressin and placebo group
- Severe AE < 1% desmopressin, 2% placebo
- No patient had serum sodium < 125mmol/L, 3 (2%) had serum sodium < 130mmol/L; of these 1 patient was < 65 years and 2 were > 65 years. All patients had levels > 130mmol/L after repeating values after 2 to 4 days without interrupting treatment.

Figure 3: Study CS40. Minimum post dose serum sodium levels by subject age (safety analysis set)

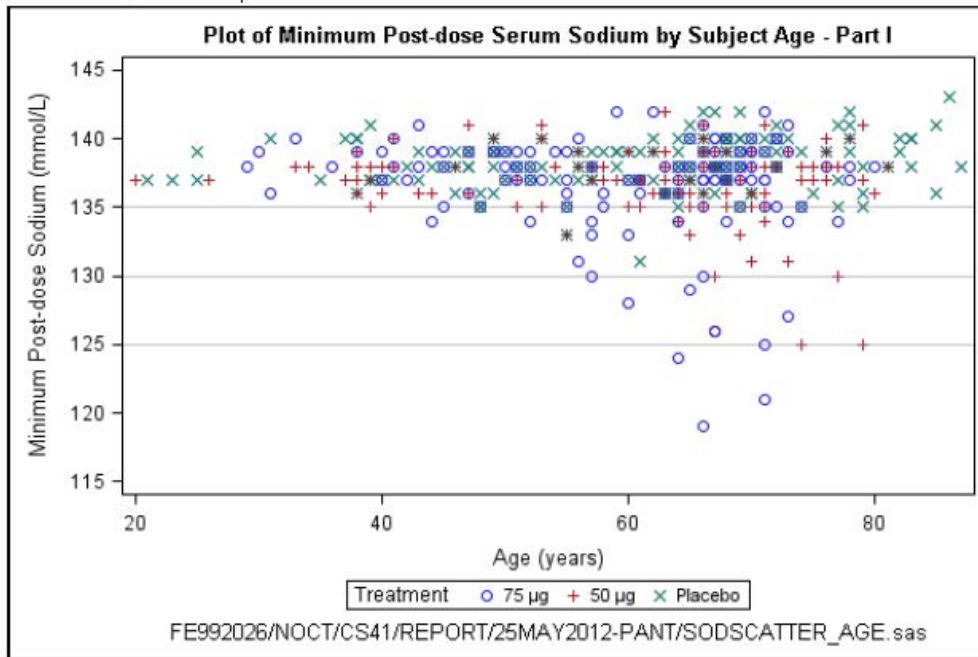


CS41

Similar pattern of AE as in CS40. The risk of hyponatremia increased with age and desmopressin dose.

Table 10: Study CS41 Risk of hyponatremia with age and dose of desmopressin

Serum Sodium Level	Placebo (N=143)		Desmopressin 50 µg (N=119)		Desmopressin 75 µg (N=122)	
	<65 years (N=75)	≥65 years (N=68)	<65 years (N=62)	≥65 years (N=57)	<65 years (N=63)	≥65 years (N=59)
≤125 mmol/L	0	0	0	2 (4%)	1 (2%)	3 (5%)
126-129 mmol/L	0	0	0	0	1 (2%)	4 (7%)
130-134 mmol/L	2 (3%)	0	2 (3%)	7 (12%)	8 (13%)	4 (7%)
≥135 mmol/L	73 (97%)	68 (100%)	60 (97%)	48 (84%)	53 (84%)	48 (81%)

Figure 4: Study CS41 Minimum post-dose serum sodium levels by subject age (Safety Analysis Set) Part I**CS29***Hyponatraemia*

A total of 34 (4%) subjects developed hyponatraemia during Part I. There was essentially no difference in the occurrence of hyponatraemia between placebo and the 10 µg and 25 µg groups; however, the incidence of serum sodium < 130 mmol/L rose from 1.3% in the 25 µg group to 7.0% in the 50 µg group and to 11.3% in the 100 µg group. During Part II, a total of 17 (3%) subjects developed hyponatraemia. 7 (6%) subjects in the 100 µg group and a total of 6 (1.5%) subjects in the combined 10 µg, 25 µg and 50 µg groups had serum sodium < 130 mmol/L. Hyponatraemia tended to occur early in treatment, usually during the first week, and was more common in subjects ≥ 65 years of age.

Table 11: Study CS29; Number (%) of subjects with hyponatraemia by age group (Part I and Part II combined)

Serum Sodium	Age Group						
	≤50 yr (N=151)	51-55 yr (N=73)	56-60 yr (N=106)	61-65 yr (N=105)	66-70 yr (N=140)	71-75 yr (N=115)	>75 yr (N=109)
<130 mmol/L	0	4 (5%)	1 (1%)	2 (2%)	8 (6%)	11 (10%)	18 (17%)
≥125 to <130 mmol/L	0	3 (4%)	0	2 (2%)	6 (4%)	9 (8%)	14 (13%)
<125 mmol/L	0	1 (1%)	1 (1%)	0	2 (1%)	2 (2%)	4 (4%)

Cross-reference: [Table 14.5.12.6] (Part II)

Post market data

Overall, most adverse reactions for desmopressin concerns subjects below the age of 18. However, for the nocturia indication, about 75% of the reports concerns subject's ≥ 65 years. For both the desmopressin tablets and oral lyophilisate, hyponatraemia is the most commonly reported adverse reaction in adults, with subject's ≥ 65 years contributing to the majority of the reports. No cases of hyponatraemia has been reported for adults < 65 years treated with desmopressin 60 µg or less in the nocturia indication, whereas 24 cases have been received concerning adults > 65 years of age. One report has been received concerning an elderly woman treated with Nocdurna 25 µg. The post-marketing data support that elderly subjects are at increased risk of developing hyponatraemia.

Risk management plan

Summary of safety concerns;

The summary of safety concerns is presented in Tables 5 and 7 above.

Pharmacovigilance: Routine (that is, passive/spontaneous reporting) is proposed.

The sponsor has been required by the European authorities to conduct a post registration safety study (the study protocol is in development) to address the following risks: hyponatraemia in elderly patients over 65 years, precipitation of congestive cardiac failure, new or worsening cardiovascular events, thromboembolic events.

Risk-benefit analysis

Desmopressin has been registered for over 20 years. Its safety depends upon the context of its use. The main risk of desmopressin is that of hyponatremia. The risk is most significant in patients who drink excessive water, or who have underlying diseases associated with SIADH or fluid retention.

The clinical trials submitted showed statistically significant improvements in the primary endpoints in a select population with a low rate of hyponatremia; thus “the quality, safety and efficacy of the goods for the purposes for which they are to be used” has been satisfactorily established.

The difficulties around the registration of this product include:

- Nocturnal polyuria is not a distinct ‘disease’ but a symptom with multiple possible aetiologies.
- Concerns about the ability to extrapolate the conditions in the clinical trials to clinical practice to ensure safe and efficacious use.

Both the evaluator and the sponsor have sought expert advice from a range of experts including urologists, urogynaecologists, and geriatricians. Several themes emerged from their responses:

- a. Nocturnal polyuria needed to be defined by 24 hour frequency volume diary
- b. Other causes of polyuria and co-morbidities need to be excluded
- c. Prescription should be from a specialist not a GP
- d. Need to monitor sodium in all patients not just those < 65 years
- e. Need to continue to monitor sodium every 3 months
- f. Concerns about use in the elderly

The Delegate made a number of amendments to the PI in attempt to address these concerns. The Delegate's impression is that the PI (and therefore Nocdurna) cannot be approved until these issues are addressed.

Summary of expert advice²⁵

Question 1

How commonly do you see nocturia due to nocturnal polyuria in your clinical practice? How do you approach the management of patients with this condition and what treatment options are currently available in Australia, in particular for nocturia due to nocturnal polyuria with no clear secondary cause?

Urologists Expert 1

Nocturia is a common urinary symptom as part of an overactive bladder and affects up to 16% adult Australian population. Nocturnal polyuria, a complex disorder of increased urine output at night can be present in up to 60% of patients with nocturia, and is often associated with various medical conditions (for example, congestive cardiac failure, chronic pulmonary disease and obstructive sleep apnoea). Clinical assessment of nocturnal polyuria requires comprehensive history taking to identify various aetiologies; a careful bladder (frequency/volume) diary; and basic investigations to screen for renal failure, urinary tract infection and diabetes. The current treatment strategies for patients with nocturia due to nocturnal polyuria include behavioural and dietary modification, removal of offending medication and use of anticholinergics for overactive bladder (or alpha-blockers in benign prostatic hyperplasia). Desmopressin is indicated for nocturnal polyuria secondary to diabetes insipidus.

Urologists Expert 2

It is important to rule out severe prostatic obstruction / other problems which may interfere with renal concentrating function. Ruling out prostatic obstruction takes some careful clinical work; the PI says "clinical examination and question". This is not sufficient. A urinary tract ultrasound is required in addition to the frequency/volume chart. Fluid management is important in this condition and even in the elderly, excessive water consumption may be a problem.

²⁵ The names of the clinical experts have been removed for confidentiality reasons and been replaced with their respective field and a number for identification purposes.

Urogynaecologists Expert 1

There is still a significant number of patients with no underlying pathology who have increased urine production and nocturia. There really is no appropriate treatment, other than synthetic antidiuretic hormone (ADH) or desmopressin in these patients.

Geriatricians Expert 1

This expert sees very few patients whom they would consider suitable for Nocdurna.

Geriatricians Expert 2

It seems unclear whether Nocdurna is intended for nocturia, nocturnal polyuria with no clear secondary cause (similar to subjects included in the clinical trials), or nocturnal polyuria excluding patients at high risk of hyponatremia (as per PI indications and contraindications). The precautions section of the PI states that 'Nocdurna treatment should only be considered when nocturnal polyuria has been established as the primary cause of nocturia' which would suggest that it is intended for nocturnal polyuria when there is no other major cause of nocturia. Yet there is a literature suggesting that nocturnal polyuria is the primary mechanism underlying nocturia in many conditions.²⁶ The contraindications section of the PI includes conditions such as the heart failure where nocturnal polyuria is part of the mechanism for nocturia. It would be helpful if the proposed Indication could be clarified for example 'for nocturnal polyuria with no clear secondary cause for nocturia and in subjects at minimal risk of hyponatremia'.

Question 2

Do the precautions in the proposed PI adequately exclude the use of Nocdurna in patients with nocturnal polyuria due to secondary causes (for example cardiovascular disease) and who may not benefit from Nocdurna?

Urologists Expert 2

The PI needs to clearly state the at risk medications; [the Urologists Expert 2] would mandate a list of drugs that place the patient at increased risk of hyponatraemia; a serious medical problem that needs to be emphasised and monitored carefully in all patients taking the drug.

Also; the polyuria needs to be documented; this takes some careful clinical work. Urinary output charts are rarely done in general practice but are necessary to determine whether nocturnal polyuria exists. ... Bladder emptying needs to be demonstrated to be adequate. A 250 mL residual volume threshold is very high (this was used in the clinical trial). If a male patient has a high residual volume he is likely to have a far greater clinical effect from Duodart or relief of prostatic obstruction. In the clinical trial urinary flow data were used to rule out significant obstruction. This is not available in general practice. A lower residual volume of 100 mL would help to minimise the potential harm from not detecting prostatic obstruction.

Urogynaecologists Expert 1

[The Urogynaecologists Expert 1] would suggest physician review for patients with other than mild, well controlled hypertension, mild renal impairment or unstable diabetes. This can also identify those patients with medical conditions which are not a contra-indication for desmopressin who can then benefit from treatment.

²⁶ Weiss JP et al Nocturia think tank: Focus on nocturnal polyuria: ICI-RS 2011 *Neurourology and Urodynamics* 2012; 31:330-339

An initial bladder diary as described above and ideally for 48 to 72 hours is an essential baseline investigation to confirm nocturnal polyuria. This is implied but needs to be explicitly stated.

Urogynaecologists Expert 2

The inappropriate use of Nocdurna for secondary causes of nocturnal polyuria will depend on the education and training of the prescriber in the management of nocturia including evaluation, investigation, diagnosis and treatment of primary and secondary causes.

[The Urogynaecologists Expert 2] expects most patients with true Primary Nocturnal Polyuria will benefit from Nocdurna. The PI does not list the differential diagnosis of nocturia or the secondary causes of nocturnal polyuria.

Geriatricians Expert 2

The 'clinical examination and questioning' recommended in the precautions section of the PI does not provide sufficient guidance. There would need to be completion of a bladder diary, blood testing (for sodium, renal and liver function), bladder ultrasound (post void residual), possibly cystoscopy (for genitourinary pathology), cardiac examination and possibly chest X-ray (for heart failure), urine testing (for infection and electrolytes) amongst possible other investigations in order to comply with the indication, contraindications and precautions and to be consistent with the exclusion criteria in the clinical trials. This approach might identify patients who are more likely to have a favourable outcome with Nocdurna.

Given the concerns about hyponatremia and the importance of the contraindications and precautions, then it is likely that only specialists in the field (for example, urologists, nephrologists, geriatricians) would have the resources, time and expertise to ensure that the indications, precautions and contraindications are complied with and that appropriate monitoring is undertaken.

Question 3

Please comment on the appropriateness of serum sodium monitoring plan in the proposed Nocdurna PI.

Urologists Expert 3

To minimise risk of subsequent hyponatremia further evaluation at 3 months and annually thereafter is warranted.

Urologists Expert 2

The plan is appropriate but must be emphasised if patients are to trial this agent. It is a more risky drug than other drugs for bladder dysfunction. Because hyponatraemia induces confusion, patients may not be aware of the reason for their illness.

Urogynaecologists Expert 1

Baseline serum sodium, within the first week and at one month is a reasonable initial protocol. However this should be advised for all patients, not just for older patients. For those patients with baseline sodium at low normal levels, it may be safer to test day 3 in case patients are exquisitely sensitive and at Day 10 followed by the one month level. [The Urogynaecologists Expert 1] would also retest patients remaining on desmopressin at three monthly intervals.

Geriatricians Expert 1

Under use in the elderly the PI states that patients over 65 should have a normal serum sodium at baseline. There should be repeat serum sodium measurements within the first 4 to 8 days and again at one month. This seems appropriate.

However it is not clear as to whether patients under 65 should have serum sodium monitoring. A number of drugs are listed that could lead to hyponatraemia in the presence of Nocdurma such as SSRIs, sulphonylureas, diuretics and it is suggested that patients on these require more frequent monitoring of serum sodium although it is not clear as to how frequent.

[The Geriatricians Expert 1] would assume that serum sodium should be checked to be normal in all patients prior to commencing Nocdurma particularly as there should be a measure of renal function prior to commencing treatment.

Geriatricians Expert 2

A more directive contraindication might be 'A history of hyponatremia or a sodium less or equal to 134 mmol/L'. This should be promoted to the second dot point in the list of contraindications as it is the probably the most important contraindication.

Question 4

The risk of hyponatraemia was satisfactorily managed in the pivotal trials (CS40/CS41; duration 3-months; carefully selected patients, who were closely monitored). Based on your experience, is the risk of hyponatraemia likely to be satisfactorily managed outside of a clinical trial, in every-day clinical practice in Australia?

Urologists Expert 3

Close clinical monitoring is burden for both, patient, clinician and the health system. However, [Urologists Expert 3] experience is that doctors who are interested in treating challenging multi-factorial conditions such as nocturnal polyuria are diligent in complying with guidelines.

Urologists Expert 1

Provided that clinicians remain vigilant about the risk of hyponatraemia with Nocdurma use, and that appropriate management strategies (including referral to endocrinologist or general physician) are instituted, the risk of hyponatraemia is likely to be satisfactorily managed outside of a clinical trial, in everyday clinical practice in Australia.

Urologists Expert 4

The hyponatraemia caused within the studies has been usually quite mild, with the only form of treatment usually required being to discontinue the medication. The symptoms of more severe hyponatraemia are usually well evident and unlikely to be missed allowing hospitalisation to be initiated quite quickly. In [Urologists Expert 4] discussions with general medical practitioners, as well as other specialists likely to be involved in managing a patient with nocturnal polyuria, there is a high awareness of the risk of hyponatraemia when using desmopressin, especially in the elderly. The Minirin formulation of the drug is far more likely (relatively) to trigger this side effect in adults (especially the elderly) and has sensitised awareness within the medical community.

Urologists Expert 2

Desmopressin has been an authority prescription. This has helped safeguard against risk by raising awareness at the point of prescription. [The Urologists Expert 2] would recommend a risk mitigation strategy such as this when prescribing this new formulation. Minimum requirements around hyponatraemia testing should be provided. The minimum criteria for monitoring as well as minimum diagnostic criteria (written evidence of nocturnal polyuria as well as demonstration of satisfactory bladder emptying with ultrasound) would reduce the risk around inappropriate prescribing (for example to patients with severe bladder dysfunction).

Urogynaecologists Expert 1

[The Urogynaecologists Expert 1] has used desmopressin for nocturnal polyuria in sensible, well-educated patients for many years and have never had a problem with significant hyponatraemia.

Urogynaecologists Expert 2

Serum sodium testing is easy to arrange and [Urogynaecologists Expert 2] believes acceptable and affordable to patients, and not a barrier to appropriate usage.

Geriatricians Expert 1

The [Geriatricians Expert 1] is hoping that Nocdurna will be initiated by specialists who are experienced in dealing with bladder problems rather than General Practitioners. The [Geriatricians Expert 1] believes the risk can be managed if there are restrictions on who is able to prescribe the medication with robust systems in place including reporting of adverse events.

Geriatricians Expert 2

In a real life observational study of desmopressin in nocturnal polyuria, hyponatremia occurred in 14% of patients, particularly if they were older.²⁷

Although sodium testing is recommended for patients 65 years and older, it would be prudent to determine sodium in younger patients especially if they develop any suspicious symptoms or are taking medicines that potentially cause hyponatremia.

A black box warning may be necessary to increase awareness of hyponatremia and to increase the likelihood that sodium monitoring is undertaken.

Question 5

Please comment on the adequacy of the Precaution in the Nocdurna PI when taking Nocdurna with medicines that may increase the risk of hyponatraemia. Is further advice needed, and if so, what would you suggest?

Geriatricians Expert 1

There appears to be a wide range of drugs that could potentiate the effect of Nocdurna and hence increase the risk of hyponatraemia. Perhaps more clarity on the degree of monitoring of serum sodium in this group and also developing a patient fact sheet with regard to notifying doctors of changes in medication as a prompt for closer monitoring.

Question 6

Please provide any other comments you may have on the benefits and harms (and associated uncertainties) around use of Nocdurna in Australian clinical practice.

Urologists Expert 3

Nocturnal polyuria is a common problem that negatively impacts upon patient's quality of life. However, the diagnosis is challenging and treatment involves a multi-disciplinary team. Once medical treatment is considered there is a very significant list of contraindications and precautions prior to commencing medical treatment that then requires significant and frequent monitoring that is a burden for all involved.

The clinical impact of the treatment is only mild to moderate with a mean decrease in nocturnal voids of 0.22 voids/night and patients being 1.85 times more likely to achieve a

²⁷ Choi E Y et al The Risk of Hyponatremia with Desmopressin Use for Nocturnal Polyuria. *American Journal of Nephrology* 2015; 41:183-190

greater than 33% reduction in nocturia than on placebo. There is also a 5 point decrease in NQOL score more than placebo. While all of these changes are statistically significant the extent of the clinical impact over placebo is a little underwhelming.

Urologists Expert 1

It appears that the benefits outweigh the risks of Nocdurna in patients with nocturnal polyuria, with statistically significant differences detected in the co-primary end-points. Nonetheless Nocdurna should be prescribed by specialists (endocrinologist and urologist) following appropriate screening and counselling of patients with nocturnal polyuria.

Urologists Expert 4

Nocturia remains one of the most significant health issues in all communities. There is a documented increase in both mortality and morbidity in those people of all ages who need to void more than two times per night (or sleep episode for shift workers). There is a significant impact on the quality of an individual's life with nocturia. It has been associated with the highest bother in both men and women reporting lower urinary tract symptoms. Of even more significance to the wider community, nocturia has also been demonstrated to have a significant impact on the quality of life of the sufferer's partner, who also often suffers from a decrease in sleep as they are disturbed by the patient's need to go to the toilet. Accessing toilets and bathrooms at night is also associated with significant morbidity, leading to an increase in "across the board" injury, but in particular hip and pelvic fractures, which have a significant mortality at 12 months as well as a 100% non-return to previous activity levels in those 70 years of age or older.

In this light, Nocdurna has the potential to provide a significant benefit to both, the individual sufferer and, the community, by decreasing nocturia in those suffering from nocturnal polyuria. It has been shown to be safe in combination use with alpha-blockade and anti-cholinergic medication; two other classes of drugs that provide significant improvement in lower urinary tract symptoms. This fact also increases its potential benefit.

The main side effect of hyponatraemia is relatively low and mild when compared to these issues.

Whilst nocturnal polyuria is by no means the only cause of nocturia, it is a significant contributor to the problem. In the light of the significant morbidity, mortality, cost to the community and effect on the quality of life of both the sufferer and their partner, [Urologists Expert 4] feels anything that can decrease the problem can bestow a significant benefit to the patient, their family and the wider community. To [Urologists Expert 4]'s assessment the potential benefits outweigh the potential risks; which are easily dealt with in the setting of appropriate awareness and prescribing habit.

Urologists Expert 2

A low dose sublingual wafer is an attractive formulation for this agent for patients with nocturnal polyuria. Relative to the current formulations that are available a 25 µg (female) and 50 µg (male) dosage would appear to reduce the risk of hyponatraemia in patients who would benefit from this drug in the treatment of nocturnal polyuria. The risk of hyponatraemia and its mitigation is critically important.

The selection of patients to rule out other health problems, particularly prostatic obstruction and other problems leading to severe bladder dysfunction in men and women is required. This is not sufficiently emphasised in the PI but is likely to be an issue as it moves from a study to a real world clinical offering.

All problematic medications were excluded in the randomised clinical trial studies. Ensuring patients are not on problematic medications is required. Ensuring patients have

normal sodium prior to initiating Nocdurna is important; it would not be difficult to make a case for all patients having a serum sodium before initiating therapy and all patients over 65 should have serum sodium before starting the drug and within a week of starting it, the sodium should be re-checked.

Urogynaecologists Expert 1

While all this monitoring and precaution may seem cumbersome and a little alarming, [the Urogynaecologists Expert 1] wants to stress that a reduction in nocturnal polyuria and resulting nocturia can be life changing. Nocturia is very debilitating. It increases the risks of falls and all the associated morbidity. Patients are chronically tired and the potential embarrassment may cause them to limit social and family interaction. We need an effective treatment for this condition and desmopressin works.

Urogynaecologists Expert 2

Nocturia is common and has significant impact on QOL including depression, sleep deprivation, falls and even mortality. Causes are often multifactorial. Treatment options for the nocturnal polyuria component or in patients with isolated primary nocturnal polyuria are very limited. There is a strong place for this product in the management of these patients.

Currently education of GP's and even specialists in the management of nocturia is often inadequate and the introduction of this product will address this issue because medical education, led by the pharmaceutical company, will inevitably follow.

Geriatricians Expert 1

Most elderly patients [Geriatricians Expert 1] sees are not too disturbed by nocturia of twice a night but often are distressed at > 2 voids per night. [Geriatricians Expert 1] has concerns of Nocdurna being used in the elderly for the treatment of nocturnal polyuria in adults who wake 2 times at night. [Geriatricians Expert 1] would recommend it only be used for 3 or more voids per night in older patients.

[Geriatricians Expert 1] has concerns about the use of Nocdurna in the frail elderly where hyponatraemia can lead to hospitalisation delirium and falls with subsequent fractures. Frail elderly patients frequently have reduced GFR.

[Geriatricians Expert 1] would have concerns about the use of Nocdurna in patients with cognitive impairment and would consider it a contraindication.

If Nocdurna is to be initiated by General Practitioners there is a risk that these patients will not have a proper continence assessment and the medication will be prescribed inappropriately.

A GFR of < 45 mL/min /1.73 m² is listed as a contraindication to Nocdurna but there is no mention of checking renal function with the sodium prior to commencing therapy.

Geriatricians Expert 2

From the clinical evaluators report and the different conclusions of the international regulatory authorities, it is apparent that there is uncertainty about the balance between benefit (reduction of nocturnal voids by one every few nights) and harms (hyponatremia in about one in ten patients). For older patients in who are prescribed medicines in this situation, it is important that safety is prioritized. In older patients, adverse drug reactions are more frequent and more serious than in younger age groups and minimizing the risk of adverse drug reactions is pivotal to ensuring good outcomes with medicines. The risk of hyponatremia is likely to be greater in older patients with multi-morbidity and polypharmacy that are more typical of 'reallife' patients with nocturia. Therefore careful selection of patients and close monitoring will be very important. If Nocdurna is

registered, this might be achieved by restricting prescribers to specialists and a black box warning.

Delegate's considerations

The FDA has not approved Nocdurna, whereas Health Canada and the Swedish National Regulatory Agency (on behalf of various other member states in the EU) have approved it.

Nocturnal polyuria is a symptom complex due to a number of contributing physiological problems. It is associated with poor sleep and poor quality of life.

The clinical trials involved a highly select subject group and showed small benefits in terms of reduced nocturnal voids. A quality of life assessment was part of studies CS40 and CS41 and showed trend towards improved quality of life. There was also a significant placebo effect.

The main safety concern is hyponatremia. The risk is small in patients < 65 years and on doses on < 50 µg but increases with age and dose.

Proposed action

The Delegate considered that approving Nocdurna with additional changes to the PI to be a safer option than rejecting the application and potentially having physicians use higher strength tablets off label for this indication.

However, the Delegate was mindful that alternate views were held by the evaluator and the FDA thus sought further advice from the ACPM.

Request for ACPM advice

The Delegate's impression is that this may be a treatment option for a select group of patients who have had secondary causes and co-morbidities excluded, have already instituted lifestyle measures, and are being managed by a specialist in this area. There may be less efficacy and more risks if this medicine is used inappropriately.

The Delegate's concern about registering this product is whether the risk mitigation strategies (PI) are adequate to ensure that the medicine is used appropriately. If not, are there any other risk mitigation strategies that could be recommended?

Response from sponsor

Introduction

Ferring notes the TGA Delegate's advice to ACPM.

Consistent with the TGA Delegate's advice to ACPM, Ferring contends that Nocdurna would be a valuable option for Australian patients seeking treatment for bothersome nocturia due to nocturnal polyuria with no apparent secondary cause and does not respond to lifestyle changes, a condition that can have a profoundly negative effect on a patient's quality of life and general wellbeing, and for which there is no available evidenced-based, approved treatments.

The Nocdurna clinical trials programme has confirmed that the product is effective. The pivotal trials demonstrated in women and in men that, compared with the respective placebo arms, nightly doses of 25 µg and 50 µg Nocdurna respectively: reduced the mean number of nocturnal voids; increased the odds of 33% responder status; increased the time to first nocturnal void; decreased the nocturnal urine volume; prolonged the initial sleep period; improved nocturia related quality of life; and improved duration of

uninterrupted sleep and sleep quality. The programme also established that the risk of hyponatraemia is acceptable with the employment of the proposed serum sodium monitoring plan in patients at risk of hyponatraemia. Ferring, however, understands the TGA Delegate's concerns about the uncertainties surrounding real-world risk and whether the re-assuring safety profile established in the clinical programme would reflect safety with use in the clinical setting.

Ferring also acknowledges that the changes to the Nocdurna PI recommended by the Delegate are intended to assist physicians in identifying suitable patients for the product, from both safety and efficacy perspectives. In principle, Ferring supports the adoption of any practical measures that will facilitate the quality use of its medicine. Therefore, Ferring would be willing to accept the main PI changes proposed by the Delegate, should the ACPM agree that these might achieve the desired objective. However, Ferring wishes to discuss in this pre-ACPM response the following PI changes recommended by the delegate:

- The increase in the minimum number of night time voids from two to three in the Nocdurna indication.
- The inclusion of a black box warning (BBW) on the risk of hyponatraemia.
- The expansion of the proposed sodium monitoring plan to include patients under the age of 65 years.
- The inclusion of ongoing serum sodium monitoring every 3 months while on Nocdurna.
- The restriction that Nocdurna should only be prescribed by physicians familiar with treating patients with nocturnal polyuria.

For the first three of these recommended changes, Ferring wishes to query whether they are warranted and necessarily in the best interest of patients taking Nocdurna or those being considered for the product. For the last two, Ferring accepts the sentiment of the changes, but wishes to propose amendments to the proposed wording. Each of the above points will be covered below in turn under its respective heading. In addition to these points, Ferring would like to discuss some other PI changes proposed by the Delegate. These will be covered under 'Other PI matters'.

Minimum number of night time voids from two to three

For the wording of the Indications section, the TGA Delegate has proposed raising the minimum number of night time voids to qualify for Nocdurna treatment from two to three. The reason for this change is unclear to Ferring, but we note that one of the external experts, a geriatrician, has recommended that Nocdurna only be used for 3 or more voids per night in older patients, on the basis that "*Most elderly patients I see are not too disturbed by nocturia of twice a night but often are distressed at > 2 voids per night.*"

Ferring questions whether this proposed change to the PI would result in better efficacy or safety compared with what was observed in the Nocdurna clinical programme, and thereby act to improve the risk-benefit ratio of the product.

By ICS definition, even a single episode of awakening to void can be defined as nocturia. However experts generally agree that nocturia is likely to be clinically meaningful if a patient voids 2 or more times nightly. For this reason, ≥ 2 night time voids was the inclusion criterion chosen for the Nocdurna clinical programme. As such, overall efficacy and safety in the programme was established in a population having this minimum number of night time voids. Indeed, just over 50% of patients who entered the two pivotal studies had between 2 and 3 night time voids at baseline; the median number of baseline voids in these studies was about 2.7. Therefore, the contribution of patients with less than

three night time voids at baseline was substantial to the overall dataset. Crucially, there is no evidence from the pivotal trials that Nocdurna would be more effective or safer in the sub-groups of patients from these trials who had three or more voids at baseline; Ferring has conducted a post hoc sub-group analysis to investigate efficacy in patients with < 3 voids at baseline against those with > 3 voids and showed no significant difference in treatment effect. Hence, increasing the minimum number of night time voids from two to three in the Nocdurna indication would, in effect, mean disregarding information from a large portion of the supporting dataset from the pivotal studies.

Moreover, Ferring would suggest that the decision for a clinician to intervene with a drug treatment in a patient with nocturia should, in principle, be based on the degree to which that individual's night time awakenings lead to bothersome sleep disturbance rather than on the minimum number of voids per night the individual experiences. While some patients may not be too bothered with an average of between two and three awakenings per night to void, such patients are unlikely seek treatment. Others in this category will be bothered sufficiently to seek treatment and Ferring questions whether such patients should be excluded from the proposed indication if they are prepared to accept the risk-benefits of Nocdurna and meet all of the other restrictions in the indication.

Black box warning on hyponatraemia risk

The TGA Delegate has recommended that the Nocdurna PI contain a black box warning with the wording:

Black box warning:

Nocdurna can cause hyponatraemia due to fluid overload. Risk factors include

- Age >65 years
- underlying medical problems such as heart failure, renal impairment, peripheral oedema, SIADH
- history of hyponatraemia
- Cognitive impairment
- Psychogenic or habitual polydipsia

Nocdurna must only be used when contra-indications, co-morbidities and secondary causes of nocturnal polyuria have been excluded. Monitoring of serum sodium is recommended (see Precautions).

A justification for the need for black box warning is not discussed in the Delegate's overview. However, Ferring notes that one of the external experts, again a geriatrician, has suggested that "A black box warning may be necessary to increase awareness of hyponatremia and to increase the likelihood that sodium monitoring is undertaken." The same expert goes on to state "...careful selection of patients and close monitoring will be very important. If Nocdurna is registered, this might be achieved by restricting prescribers to specialists and a black box warning."

Ferring accepts fully that the potential for hyponatraemia is the most important safety concern with Nocdurna and that the risk of this adverse effect is raised in the populations identified in the proposed black box warning. However, for the reasons discussed in this section, Ferring wishes to discuss whether the inclusion of a black box warning in the Nocdurna PI is appropriate.

Ferring is not aware of other products that have a black box warning in their PI to warn against a raised risk of hyponatraemia. However, Ferring has extensively investigated the literature to determine the level of hyponatraemia risk of some other, commonly used drugs or drug classes, and found the following reported rates: 0.5 to 32% for selective

serotonin uptake inhibitors; 11 to 30% for thiazide diuretics; and 4.8 to 40% for the anti-epileptic, carbamazepine. By comparison, the incidence of clinical significant hyponatraemia (< 130 mmol/L) reported for desmopressin in the original high dose NOCTUPUS trial in nocturia was 4 to 8%, and 2 to 4% in the Nocdurna programme. Moreover, a hyponatraemia rate of 5.6% has been reported in two systemic reviews of published desmopressin studies in nocturia.^{28, 29} Given that there are some commonly available drugs which are associated with similar risks of hyponatraemia to desmopressin in nocturia, but do not have a BBW, it would seem inconsistent and precedential for Nocdurna in Australia alone to have a BBW related to this side effect.

As indicated above, the two pivotal Nocdurna trials reported hyponatraemia rates of the order of 2 to 4%, not much higher than that seen in the control arm, and well within the incidence ranges of other drugs known to be associated with hyponatraemia. While there may be uncertainty in translating the level of risk observed in a clinical trial programme with use in clinical practice, Ferring believes that the risk of hyponatraemia with Nocdurna would be maintained at an acceptable level in clinical practice should the product be registered in Australia. Desmopressin has been available in Australia since 1977 and its pharmacological profile as an anti-diuretic is well known and understood by clinicians, including its potential to cause hyponatraemia, as this side effect arises as a direct consequence of drug's anti-diuretic effects. Ferring remains confident that Australia physicians, in particular those who treat lower urinary tract conditions and the elderly, would largely be well aware of the risk of hyponatraemia with desmopressin, and therefore, would be eager to embrace and follow any risk mitigation advice for Nocdurna. Moreover, should Nocdurna become available in Australia, Ferring is committed to promoting the product responsibly, including making widely available educational material which emphasises the importance of appropriate patient selection and serum sodium monitoring in at-risk patients, like the elderly.

A concern that Ferring has with the black box warning is that it might lead to an inappropriate level of alarm among potential prescribers and thereby act as an overall deterrent to prescribing of the product, even for younger fit patients, who are not necessarily the subject of the black box warning. This concern should not be interpreted as Ferring disagreeing with the advice given in the black box warning. Indeed, if the ACPM decides that a black box warning is not required, Ferring is prepared to include the text from the black box warning at the beginning of the Precautions section of the PI; our draft PI has been amended accordingly. If, on the other hand, the ACPM considers that the proposed black box warning is warranted, Ferring is prepared to accept its inclusion in the Nocdurna PI, as indicated in the Introduction of this response document.

It is worth noting that, as part of the approval of Nocdurna in the EU, Ferring is conducting a Post-Authorisation Safety Study (PASS) to assess the real world safety of Nocdurna. Ferring is willing to give an undertaking to submit the results of the PASS to TGA for evaluation. Then, if a black box warning were to be mandated as part of the initial approval of Nocdurna, Ferring would then apply to have the black box warning removed should the PASS confirm that the hyponatraemia risk is acceptably low outside of a controlled clinical trial setting.

Routine sodium monitoring in patients under the age of 65 years

The TGA Delegate has recommended that routine serum monitoring also be mandated in the Nocdurna PI for patients under the age of 65 years. It would appear that this proposed

²⁸ Ebell M H et al. A Systematic Review of the Efficacy and Safety of Desmopressin for Nocturia in Adults *J Urol* 2014;192:829-835

²⁹ Rembratt A et al. Desmopressin Treatment in Nocturia; an Analysis of Risk Factors for Hyponatremia *Neurourol Urodyn* 2006; 25:105-109

change is derived from one of the six themes that the Delegate has consolidated from the external experts' responses:

d) Need to monitor sodium in all patients not just those < 65 years

However, on close inspection of all the external expert responses provided, Ferring could not find where any of the experts have explicitly recommended routine monitoring in all patients under 65 years of age. The closest to a recommendation we found came from two experts, who wrote:

Although sodium testing is recommended for patients 65 years and older, it would be prudent to determine sodium in younger patients especially if they develop any suspicious symptoms or are taking medicines that potentially cause hyponatremia.

Ensuring patients have normal sodium prior to initiating Nocdurna is important; it would not be difficult to make a case for all patients having a serum sodium before initiating therapy serum

To address these recommendations, Ferring would be prepared to include in the PI advice that all patients < 65 years of age should have a single baseline sodium determination before starting Nocdurna, to exclude any sub-clinical hyponatraemia. The advice to check serum sodium in case of clinical condition changes and when starting on a concomitant medication that can cause hyponatraemia is already covered in the PI for all patients, irrespective of age.

Overall, Ferring questions the value of routine monitoring of all patients < 65 years of age in period after commencing Nocdurna (that is at 1 week then at 1 month). In the Nocdurna pivotal trials, post-dose serum sodium concentration was investigated closely in all patients. In the sub-groups of patients < 65 years of age administered nightly doses of 25 µg (women; n = 71) and 50 µg (men; n = 62) the incidence of hyponatraemia was very low at 2%: there were two cases detected in women, one mild (130 to 134 mmol/L) and one clinically significant (126 to 129 mmol/L), and two mild cases in men. All of these shifts in serum sodium were transient and did not result in patients discontinuing from the studies. In view of these reassuring findings, it would seem an unnecessary burden for all patients < 65 years of age to undergo routine serum sodium testing at 1 week, then 1 month after commencing Nocdurna.

However, if the ACPM considers that routine monitoring of all patients in the period after commencing Nocdurna is warranted, Ferring is prepared to accept provisions for this recommendation in the PI.

The proposed advice on sodium monitoring in the draft PI is outlined below:

Under Precautions:

Sodium Monitoring:

All patients should receive a single baseline sodium determination before starting Nocdurna. Sodium should be measured every 3 to 6 months and/or when medications are altered or the patient's clinical condition changes.

Patients 65 years and older should receive additional monitoring of sodium during the first week of treatment (4 - 8 days) and again at one month.

Under Precautions/Use in the elderly and Dosage and Administration/Special populations/Use in the elderly

In elderly patients (65 years of age and older), serum sodium should be within the normal range before initiating treatment, in the first week (4 to 8 days after initiation), at one month, at 3 to 6 months and/or when medications are altered or the patient's clinical condition changes.

Ongoing serum sodium monitoring every 3 months

Ferring accepts the TGA Delegate's proposal to include guidance in the PI for regular ongoing monitoring of serum sodium while a patient is taking Nocdurna long term. However, Ferring questions whether a fixed recommendation of every three months is appropriate and necessary for all patients.

For an elderly patient with multiple inter-current diseases, it would seem reasonable to check serum sodium every three months, whereas in an otherwise fit young individual, requiring a blood test every 3 months would appear an unnecessary inconvenience, given the relatively low risk of hyponatraemia in such patients. With this in mind, Ferring wishes to propose that, rather than routine monitoring every three months for all patients, the recommendation be changed to reflect ongoing monitoring every 3 to 6 months, depending on clinical need. The draft PI has been changed accordingly.

In support of the 6 month upper value of this range, Ferring notes that, in a recent independent review article on nocturia by a group of experts in the field, a recommendation for ongoing sodium monitoring every 6 months is given for patients with nocturia on long-term desmopressin.³⁰ See above for the proposed sodium monitoring advice.

Restrict prescribing to physicians familiar with treating patients with nocturnal polyuria

The TGA Delegate has proposed that the PI statement

Nocdurna should be prescribed only by physicians familiar with treating patients with nocturnal polyuria. Treatment should only be initiated after contra indications, secondary causes of polyuria and bladder outlet obstruction have been excluded. Monitoring of serum sodium is recommended (see PRECAUTIONS).

Ferring consider that singling out a group of prescribers with expertise in the treatment of nocturnal polyuria is somewhat obscure, given that nocturnal polyuria is strictly not a disease. Also, information in the second sentence appears to conflict with advice given elsewhere in PI on bladder outlet obstruction. In view of these issues, we suggest the following alternative wording:

Nocdurna should be used under the guidance of physicians familiar with the diagnosis and management of nocturia. Treatment should only be initiated after contra indications, secondary causes of polyuria and bladder outlet obstruction have been considered (see PRECAUTIONS).

The new wording identifies a group of physicians who are able to investigate the cause(s) of a patient's nocturia, whether it be due to nocturnal polyuria or other causes. It also allows other, more accessible, clinicians, such as a patient's GP, to take care of day to day management, such as the monitoring of the patient's serum sodium levels, under the guidance of an expert.

Other PI matters

In this section Ferring would like to deal with two other PI related matters.

The TGA Delegate has included "Peripheral oedema" as a contraindication. Ferring, however, has removed this as a contraindication in the draft PI because

1. Peripheral oedema related to fluid imbalance would result from "A history of known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics", which is listed as a Contraindication, and

³⁰ Dani H et al. Nocturia: aetiology and treatment in adults *Nature Rev Urol* 2016; doi:10.1038/nrurol.2016.134

2. “peripheral oedema” appears as a precaution in the text of the black box warning.

The Delegate has proposed that the original Precautions statement “*Fluid intake must be limited to a minimum from 1 hour before administration until the next morning (at least 8 hours) after administration.*” be changed to “.1 hour before administration until urine is passed the next morning.” The original wording has been kept in the draft PI because the proposed new wording may be misinterpreted. If patient were to wake very early in the morning and pass urine, a real possibility with nocturia, and then drink copious amounts, as appears to be permitted by the new wording, it could be dangerous as the effects of desmopressin may not yet have worn off. For this reason it is prudent to recommend waiting the full 8 hours.

Conclusion

The most important risk minimisation feature to come out of the Nocdurna programme was a rigorous characterisation of gender specific, minimum effective doses of desmopressin for use in nocturia. The proposed nightly doses, 25 µg for females and 50 µg for males, are considerably lower than those recommended overseas for earlier oral dose forms of desmopressin approved in nocturia. The programme demonstrated in well conducted, placebo controlled trial that Nocdurna is effective in decreasing the number of night time voids patients experience; in addition to improving sleep related outcomes and patient quality of life.

The risk of hyponatraemia with Nocdurna was show to be acceptably low in the programme. As part of the programme, the sodium monitoring plan for patients at risk of hyponatraemia was developed and tested. In translating the safety profile established in the Nocdurna programme to real world use of the product, Ferring contends that desmopressin is well known and well understood by Australia clinicians and that, should Nocdurna be approved, local physicians would be eager to adopt all recommended measures designed to mitigate against this risk.

Ferring acknowledges that, with Nocdurna, appropriate patients selection is crucial from both efficacy and safety perspectives, and that prescriber-education on this is an important facet of making this product available, should it be approved in Australia. As an example to Ferring’s commitment here, we have provided substantial financial support to an independent, world class research project at Royal Melbourne Hospital to develop and validate a short clinical tool, called TANGO, which is designed to assist a physician in the clinic in identifying the cause(s) of a patient’s nocturia. TANGO is now entering the clinical testing phase and is intended to be used in conjunction with a frequency voiding chart.

Nocturia can be very detrimental to quality of life (QoL) in patients who regularly have multiple night time voids. In those whose nocturia is due to nocturnal polyuria with no obvious secondary cause and cannot be controlled by lifestyle changes, no effective treatment option currently exists in Australia. For such patients, Ferring considers that the availability of Nocdurna would help address an important clinical need. Ferring notes that similar sentiments are expressed by a number the external experts who provide comment to TGA.

Finally, as is apparent from the comments of some of the external experts, Minirin (desmopressin) is currently being prescribed “off-label” in Australia for the treatment of nocturia. Indeed, in recent years, coinciding with the publication of the Nocdurna pivotal results, Medical Information at Ferring Australia has fielded an increased number of enquiries from Australian physicians asking about the use of Minirin tablets (200 µg) and melt (120 µg and 240 µg) in nocturia. To answer these enquiries, Ferring stresses that such use is unapproved in Australia, then defaults to providing information related to Minirin use from those countries that have the nocturia indication approved. It is Ferring’s understanding that some clinicians prescribe the overseas approved nocturia dosages (60

to 240 µg at night for melt or 100 to 400 µg at night for tablet), while others recommend to patients that they cut the tablet or melt for their night time dose, for example quartering a 200 µg tablet, in an attempt to approximate the Nocdurna 25 µg and 50 µg doses. We are also aware of isolated cases where Minirin spray has been prescribed for nocturia. Should Nocdurna become available in Australia, such uncertainties associated with off-label use would largely be overcome. Also, the approval of Nocdurna would permit Ferring to embark on a suitable education campaign to physicians on the selection of appropriate patients for the product, both from safety and efficacy perspectives.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA Delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Nocdurna sublingual wafer containing 25 µg and 50µg of desmopressin to have an overall positive benefit–risk profile for the amended indication;

Nocdurna is indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken three or more times a night to void

In making this recommendation the ACPM

- noted that Nocdurna may have clinical benefit in a carefully selected patient population.
- noted that desmopressin is used as an off label therapy in the treatment of nocturnal polyuria Nocdurna would be a more appropriate dose formulation.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- CMI should highlight that Nocdurna is indicated for a 'carefully selected' patient population with idiopathic nocturia.
- PI should be clearer about the potential problem of concomitant medications, monitoring in all patients regardless of age.
- PI/CMI should highlight the need to monitor therapy when introducing or changing the dose of concomitant medication, or there is a change of clinical condition.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *This may be a treatment option for a select group of patients who have had secondary causes and co-morbidities excluded, have already instituted lifestyle measures, and are being managed by a specialist in this area. There may be less efficacy and more risks if this medicine is used inappropriately. There are concerns about registering this product*

whether the risk mitigation strategies (PI) are adequate to ensure that the medicine is used appropriately. If not, are there any other risk mitigation strategies that could be recommended?

The ACPM agreed that Nocdurna treatment should be initiated by a specialist experienced in the diagnosis and treatment of nocturia and the use of desmopressin. It was acknowledged that more than one specialist may be involved in these patients. They recommended that the diagnosis of idiopathic nocturia be supported by a 48 hours urine diary. Treatable causes of nocturia must be excluded prior to commencing Nocdurna therapy, and contraindications must be carefully considered. The indications should specify use in patients who waken three or more times each night.

Sodium levels must be monitored in all patients, 1 week and 1 month after starting therapy, and every 3 months thereafter. Elderly patients (especially patients over 75 years) need a careful risk/benefit assessment before commencing therapy and also may require closer monitoring on an individual basis.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Nocdurna desmopressin 25 micrograms and 50micrograms (as acetate) sublingual wafers blister pack indicated for:

Nocdurna is indicated for the treatment of nocturia due to idiopathic nocturnal polyuria in adults who awaken two or more times each night to void and have not responded to lifestyle measures.

Nocturnal polyuria should be confirmed on the basis of a 24 hour urine frequency volume diary. It is defined as > 33% of urine passed overnight. Secondary causes of nocturia should be excluded (see CONTRAINDICATIONS and PRECAUTIONS).

Specific conditions of registration applying to these goods

1. Pursuant to sections 14 and 14A of the Act, I [the Delegate] hereby grant exemption for the above products from compliance with the standard for “Registered tablet or capsule without an individual British Pharmacopoeia monograph” with regard to the lower assay expiry limit as described in Section 11(b) of Therapeutic Goods Order 78. The conditions for this consent under the Act are all of the following:
 - Assay limits of 90.0 to 110.0% at expiry are approved for the products, and
 - This exemption applies for one year from the date of approval of the products.
2. The Nocdurna (desmopressin) EU Risk Management Plan (RMP), version 3.0, dated 23 February 2016 (data lock point 30 November 2015) with Australian Specific Annex version 3.0 dated 12 August 2016, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Nocdurna approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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