

Public Assessment Report

Scientific discussion

Nocdurna
(desmopressin acetate)

SE/H/1507/01-02/DC

This module reflects the scientific discussion for the approval of Nocdurna. The procedure was finalised on 2016-04-22. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Ferring Läkemedel AB has applied for a marketing authorisation for Nocdurna 25micrograms 50 micrograms, oral lyophilisate. The active substance is demopressin acetate which is a synthetic analogue of naturally occurring anti-diuretic hormone arginine vasopressin (AVP). Dessmopressin acetate reduces urine production.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Desmopressin is a synthetic structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in the deamination of cysteine and substitution of L-arginine by D-arginine. This results in a considerably longer duration of action and a lack of pressor effect in the dosages clinically used. The indication applied for is “Treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void”.

Desmopressin is a widely used, well-known active substance, and has been marketed since 1972. The nonclinical program refers to a large extent to study reports from studies performed by MAH's partner in Japan (Kyowa Hakko Kogyo). Since the nonclinical information varies in quality mainly depending on the age of the studies, the overview also includes summaries of relevant literature where appropriate. The pivotal toxicology studies were performed under GLP conditions.

III.2 Pharmacology

Desmopressin acts as a potent, selective agonist at the V2-receptor, a member of the G-protein coupled receptor super-family. After V2 receptor activation, aquaporin 2 channels (AQP2) becomes phosphorylated and inserted in the apical surface of cells in the collecting tubules of the kidney. As a V2-agonist, desmopressin causes a decreased water diuresis (antidiuretic effect) as its primary pharmacodynamic effect. Antidiuretic activity of desmopressin has been demonstrated in several animal models in different species including the oral water load model in rats.

In safety pharmacology studies, intravenous administration of desmopressin at 25 to 100 µg/kg caused increases in mean arterial pressure, whereas no adverse effect on cardiovascular function was observed at 2.5 µg/kg. Estimated exposure (AUC) margins to clinical therapeutic exposure were, however, more than 100-fold. Desmopressin induced no significant findings in standard CNS functional behavioural tests (e.g. Irwin screen and locomotion measurements), indicating that desmopressin does not penetrate the blood-brain barrier to cause CNS-effects.

III.3 Pharmacokinetics

In pharmacokinetic and toxicokinetic studies with desmopressin radioimmunoassay (RIA) was used for the analysis of plasma samples. Following oral administration to the rodent and non-rodent species used in toxicology studies (rat and dog), desmopressin was rapidly absorbed with T_{max} generally occurring within 0.5 to 1 hours. Desmopressin demonstrates low oral bioavailability which in the rat was 0.12-0.19%, 0.48-0.83% in the dog and 0.37-0.63% in the pig. In toxicokinetic studies systemic exposure increased in a dose-proportional manner in rats and a slightly greater than dose-proportional manner in rats and dogs with no differences between male and female animals and with no indication of accumulation following repeated administration.

Only slight placental transfer of desmopressin took place in pregnant rats.

Desmopressin was not metabolised by hepatic microsomes and did not display any inhibitory effect on cytochrome P450 enzymes.

III.4 Toxicology

Single dose toxicity studies using the i.v and s.c route has been performed in the mouse, rat, guinea pig, rabbit and beagle dog at doses up to 2000 µg/kg. No mortality or salient adverse effects were observed.

Repeated dose toxicity studies have been performed using the rat, rabbit and beagle dog applying both the oral, intravenous and subcutaneous routes of administration for treatment periods of 2-26 weeks duration at doses up to 238 µg/kg/day. The studies in the rat and the beagle dog following oral administration are considered as the most relevant studies for this application. The kidney was identified as a target organ. An increase in kidney weight was observed in nearly all repeated dose toxicity studies. This observation could be ascribed to exaggerated pharmacological effect. The established margins of exposure to the clinic ranging from 18 to 423 are considered sufficient.

Desmopressin was negative in the Ames test and in the Mouse Lymphoma Assay. No in vivo genotoxicity study was submitted and no carcinogenicity studies have been performed with desmopressin. However, based on the nature of the compound, the negative results in the in vitro studies and the lack of pre-neoplastic findings in the repeated-dose toxicity studies this is accepted. Desmopressin is considered as a non genotoxic compound with a low risk for carcinogenicity.

A fertility and embryonic developmental toxicity study applying the subcutaneous route of administration was carried out in rats. In this study there were no signs of adult toxicity, no effects on parental fertility and no effects on the F1 progeny at any dose level.

In a developmental toxicity study in rats the females were treated from gestational day 7 till 17 by intravenous administration. Effects of treatment were partly evaluated following Caesarean section on day 20 and partly following natural birth and up-bringing until day 21 after birth. There were no effects on the dams. Foetal survival, growth and morphology was unaffected by treatment as were post-natal offspring survival, growth development, behaviour and reproductive performance.

Two teratogenicity studies have been performed in rabbits after subcutaneous administration. The females were treated with desmopressin from gestational day 6-18 and the effects on development evaluated after Caesarean section on day 28. In one study evaluation was also performed following natural birth and upbringing, weaning and growth until the pups were 6 weeks of age. There were no effects of treatment on the dams, and foetal survival, growth and morphological development in any of the studies. Also, there were no effects on parturition, or postnatal survival, growth, development and behaviour.

A pre- and post-natal study was performed in rats applying the subcutaneous route of administration. The dams were treated with desmopressin from day 17 after mating to day 21 after parturition. There were no effects of treatment on dams during the pregnancy period. Gestation length, parturition and lactation were also unaffected. There were no effects on live birth index and subsequent viability of offspring. However, weight gain of both male and female offspring of mothers receiving 200 µg/kg/day was slightly lower than that of controls, and there was a weight-related delay in vaginal opening in female offspring at this dose level. In all other respects, offspring growth, development, behaviour, and reproductive performance the animals were unaffected by treatment with desmopressin.

There were no toxicokinetic measurements reported in any of the reproductive toxicity studies. However, exposure in the rat was estimated based on AUC values obtained in the single-dose pharmacokinetic studies. Assuming linear kinetics the exposure margins to clinical exposure are several thousandfold. Toxicokinetic in the rabbit is lacking.

The local tolerance of the mucous membrane of the cheek pouch to desmopressin-containing orally disintegrating tablets was investigated in the Syrian Hamster. There were no local reactions observed and it can be concluded that the desmopressin-containing orally disintegrating tablets were well tolerated.

Overall there are no apparent safety pharmacology or toxicology concerns in relation to desmopressin.

III.5 Ecotoxicity/environmental risk assessment

The Applicant has provided a justification for not conducting an ERA. This is acceptable. Desmopressin is a nonapeptide and an ERA is not required.

III.6 Discussion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. In conclusions, there are no concerns to approve Desmopressin from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

No PK data after treatment with Nocdurna® oral lyophilisate 25 or 50 µg are available. The current submission is based on PK evaluation of desmopressin following higher doses using Minirin® oral and sublingual tablets.

Desmopressin is a cyclic nonapeptide and received its first marketing authorisation in 1972 (DK). The studies included in the clinical pharmacology package are up to >15 years old.

Bioanalysis

During 1995 to 2005, the Applicant developed and pre-validated a RIA assay for determination of desmopressin human in plasma.

Absorption

The absolute bioavailability (F) following sublingual administration was determined to be <1%.

The relative F of the sublingual tablet compared to the conventional Minirin® tablet was 1.5.

Distribution

The volume of distribution is determined to 26-36 L.

Desmopressin has been shown to be distributed in to the breast milk of nursing mothers with <0.005% following a nasal dose.

Elimination

About 45% of iv dose was excreted in the urine.

Metabolism

Desmopressin was rather stable in human liver microsomes with about 85% remaining unchanged after 60 min incubation.

Dose proportionality

Dose proportional increase in exposure has been seen following sublingual doses up to 60-800 µg.

Time dependency

No data provided.

Intra- and inter-individual variability

High intra- and inter-individual variability have been seen following sublingual administration, about 25% and 50%, respectively.

PK in target population

No data provided.

Special population

No PK data in patients with hepatic impairment are provided.

Renal clearance (CL) as well as total CL decreased with the degree of renal function. The $t_{1/2}$ was about 3-times longer in subjects with severe compared to normal renal function.

No conclusions can be drawn with respect to potential change in PK with age considering the limited number of subjects and the unknown distribution of age in the studies submitted.

Based on limited number of subjects, higher plasma levels were seen in females compared to males following treatment with the same dose. However, gender was not identified as a significant covariate influencing the PK of desmopressin when corrected for body weight. Given these findings, it is unclear whether the gender related PD response which is underlying the proposed doses used in phase III is maintained if weight is included as a covariate in the analysis of PD data (*c.f.* section pharmacodynamics).

Interactions

Desmopressin 10 µM (≈11 µg/ml) did not inhibit human CYP 450 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4 activity *in vitro*.

No *in vivo* drug-drug-interaction data have been provided.

PKPD relationship

No data have been provided.

IV.3 Pharmacodynamics

The mechanism of action for desmopressin is well known. The Applicant's arguments for not providing extrapolating from previous data on PD are accepted. Only one PD study has been submitted with this application (study CS030). This study explores the bioequivalence between 60 µg oral lyophilisate versus 100 µg tablet desmopressin based on PD endpoints.

Different oral doses of tablet desmopressin (200 µg, 400 µg, or 800 µg) in the phase II study 45A07-37 did not show any significant difference regarding nocturnal voids or in number of voids over 24 hours. Inclusion of subjects with varying type of severe daytime voiding problems, giving a heterogeneous group, and limited sample size could be reasons.

The presented data from Study FE992026 CS029 shows age - and gender differences in the risk of hyponatraemia and the response regarding nocturnal urine volume. A significantly higher risk of hyponatraemia for women > 50 years at the 50 µg dose, and a significant decrease in nocturnal urine volume already at the 25 µg dose of desmopressin in women was observed. In women, there was no increase in effect at higher doses beyond 25 µg of desmopressin. A desmopressin dose below 25 µg was not superior to placebo irrespective of age or gender.

The MAH has justified the minimum recommended desmopressin oral lyophilisate dose for women with nocturia as being 25 µg, and the corresponding dose recommendation for men as 50 µg.

IV.4 Clinical efficacy

The efficacy of desmopressin has been studied in an extensive clinical program and the product has been marketed since more than 40 years. The main rationale for the development of the oral lyophilisate 25 mcg and 50 mcg was to identify a dose that could provide a broader safety margin, especially in elderly patients (i.e. ≥65 years).

The new low-dose, gender-specific Nocturna programme includes four Phase 3 desmopressin oral lyophilisate nocturia studies, CS29, CS31, CS40 and CS41.

The four Phase 3 studies were multicenter, randomized, placebo-controlled, parallel groups using four - one treatment arms of desmopressin (10 µg, 25 µg, 50 µg, 75 µg or 100 µg taken once per night approximately 1 hour prior to bedtime). Subjects from two of the Phase 3 studies were enrolled in two open label 1-34 month/s extension studies.

Overall 1443 subjects received at least 1 dose of the trial drug in the Phase 3 trials. The Applicant provided the number of individuals in different age strata above 65 years of age. Of the 827 subjects > 65 years, the vast majority, 645 subjects (44.7%) were > 65 – 75 years old. The numbers > 75 years were 175 (12.1%) and only 7 subjects (0.5%) were older than 85 years.

To substantiate a gender difference further efficacy analyses stratified for weight and age were presented. The Emax dose-response model shows that a gender difference is still significant after adjusting for weight. The gender-specific dosing in CS40 and CS41 trials are based on the CS29 trial. The results from the ANOVA model for CS29, including both gender and weight in the model, show that weight has a remaining impact on the endpoint, however less pronounced, than from the model with only weight included, and gender excluded and most of the difference in response is explained by gender. The provided data on change from baseline in nocturnal volume in female and male patients following treatment with 25 and 50 µg desmopressin, respectively, do not indicate a large impact of weight on response and the applicant has further justified the reasons for choosing a gender specific dosing.

The co- primary efficacy endpoints were change from baseline to final visit in mean number of nocturnal voids and proportion of subjects with >33% reduction in the mean number of

nocturnal voids. The Part II of the study CS29 and CS31 investigated the durability of desmopressin treatment.

Important secondary endpoints were dose-dependent improvements including increases in FUSP/duration of time to first void and decreases in nocturnal urine volume.

The responder status at 1 week, 1 month, and 2 months was assessed by the 3-day diary in CS40 and CS41.

In conclusion, the low-dose, gender-specific Nocdurna programme provide results for the co-primary efficacy endpoints: change from baseline to final visit in mean number of nocturnal voids and proportion of subjects with >33% reduction in the mean number of nocturnal voids. The results were similar when subjects were stratified by age (< 65yrs, > 65yrs). The results of the studies support a significant effect of the 25 µg dose among females. A dose dependant effect was reported on the co-primary endpoints for men with the 50-100 µg doses. The applicant provided further efficacy analyses stratified for weight and age. The provided data on change from baseline in nocturnal volume in female and male patients following treatment with 25 and 50 µg desmopressin, respectively, do not indicate a large impact of weight on response and the applicant has further justified the reasons for choosing a gender specific dosing.

IV.5 Clinical safety

IV.6 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Nocdurna.

Safety specification

Summary table of safety concerns in RMP (specifically for Nocdurna)

Important identified risks	Hyponatraemia in elderly patients ($\geq$ 65 years old)
Important potential risks	Precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency
Missing information	Long term use in elderly patients

Pharmacovigilance Plan

Table of on-going and planned additional PV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Non-interventional Post Authorisation Safety Study with NOCDURNA, category 3	To describe the risk of hyponatraemia events, as well as cardiovascular and thromboembolic events in patients with nocturia due to nocturnal polyuria treated with NOCDURNA and to collect long term data in elderly patients	Hyponatraemia in elderly patients ≥ 65 years. Precipitation of overt congestive cardiac failure. New occurrence or worsening of existing cardiovascular and thromboembolic events in nocturia patients treated with NOCDURNA. Long term use in elderly patients	In planning phase	Final study report planned for 2023

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the Risk Minimisation Plan

Summary of Safety Concerns and Planned Risk Minimisation Activities in RMP (for Nocdurna)

Safety concern	Routine pharmacovigilance	Additional pharmacovigilance activities	Routine risk minimisation	Additional risk-minimisation activities
Important identified risk				
Hyponatraemia in elderly patients (≥ 65 years old)	Yes	Yes (PASS)	Labelling Section 4.2, 4.4, 4.5 and 4.8. The risk of developing hyponatraemia is addressed in the CCDS/SPC in section 4.4 "Special warnings and precautions", in section 4.5 "Interaction with other medicinal products and other forms of interaction" and in section 4.8 "Undesirable effects". Ongoing safety surveillance: scheduled review and analysis of	No

Safety concern	Routine pharmacovigilance	Additional pharmacovigilance activities	Routine risk minimisation	Additional risk-minimisation activities
			cases on annual basis in connection with yearly PSUR	
Important potential risks				
Precipitation of overt congestive cardiac failure in patients with compensated cardiac insufficiency	Yes	Yes (PASS)	Labelling Section 4.3: Use in patients with current or past history of known or suspected congestive heart failure or other medical conditions associated with fluid overload is contraindicated. Ongoing safety surveillance: scheduled review and analysis of cases on annual basis in connection with yearly PSUR	No
Missing information				
Long term use in elderly patient	Yes	Yes	Labelling section 4.2 and 4.4 The risks with desmopressin in elderly patients are addressed in the CCDS/SmPC in section 4.2 Posology and method of administration, Special populations, and in section 4.4 “Special warnings and precautions”	No

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Nocdurna 25micrograms 50 micrograms, oral lyophilisate is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

Description	Due date
Non-interventional Post Authorisation Safety Study with NOCDURNA	Final study

<u>Objectives:</u> To describe the risk of hyponatraemia events, as well as cardiovascular and thromboembolic events in patients with nocturia due to nocturnal polyuria treated with NOCDURNA and to collect long term data in elderly patients <u>Safety concerns addressed:</u> Hyponatraemia in elderly patients ≥ 65 years. Precipitation of overt congestive cardiac failure. New occurrence or worsening of existing cardiovascular and thromboembolic events in nocturia patients treated with NOCDURNA. Long term use in elderly patients PASS included as a category 3 study in the RMP	report planned for 2023 Progress and any emergent safety data to be reported once a year
--	--

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Mutual recognition/Decentralised procedure for Nocdurna 25micrograms 50 micrograms, oral lyophilisate was positively finalised on 2016-04-22.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)