Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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desmopressin 25 microgram, 50 microgram oral lyophilisate (Noqdirna®)

SMC No. (1218/17)

Ferring Pharmaceuticals Ltd

13 January 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

desmopressin (Noqdirna®) is not recommended for use within NHS Scotland.

Indication under review: Symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults.

Two phase III, placebo-controlled studies demonstrated that desmopressin, at licensed doses over three months, significantly reduced the mean number of nocturnal voids and resulted in higher proportions of responders compared with placebo, in patients with nocturia.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 13 February 2017

Indication

Symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults.[1, 2]

Dosing Information

Women: desmopressin 25 microgram daily, one hour before bedtime, administered sublingually without water.[1]

Men: desmopressin 50 microgram daily, one hour before bedtime, administered sublingually without water.[2]

Product availability date

October 2016.

Summary of evidence on comparative efficacy

Desmopressin acetate is a synthetic analogue of arginine vasopressin, which mimics its antidiuretic action. Desmopressin (Noqdirna®) is formulated as an oral lyophilisate (orally disintegrating tablet) which is administered by placing under the tongue, without water, one hour before bedtime. The dose is gender specific.[1,2]

Nocturia has multi-factorial aetiology and pathogenesis, including nocturnal polyuria, and is considered to have a detrimental impact on health when at least two nocturnal voids occur, mainly due to broken sleep. Nocturnal polyuria is associated with decreased secretion of arginine vasopressin and is defined as nocturnal urine output greater than 20% to 33% of 24-hour output, depending on age.[3,4] The submitting company has requested that SMC considers desmopressin oral lyophilisate (Noqdirna®) in patients aged 65 years and over.

Evidence of efficacy for the oral lyophilisate formulation come from two pivotal phase III placebo-controlled, three-month studies conducted in females (study CS40) and males (study CS41) aged ≥18 years with nocturia, defined as at least two nocturnal voids, determined via a three-day bladder diary. Patients on stable doses of overactive bladder treatments (for at least three months) were permitted to enter the study. Patients were randomised equally to desmopressin 25 microgram or placebo (in study CS40), or desmopressin 50 micrograms [licensed dose in males], desmopressin 75 micrograms or placebo (in study CS41), stratified by age (<65 years, ≥65 years). Treatments were taken one hour before bedtime and patients were also instructed to empty the bladder before bedtime, drink to satisfy thirst only, and limit evening intake of coffee, tea, caffeinated soft drinks and alcoholic beverages.[3-5]

The co-primary endpoints were change from baseline in mean number of nocturnal voids and 33% responder status during three months of treatment, using a longitudinal analysis. This involved a repeated measures analysis of co-variance (ANCOVA) comparing change from baseline with visits at week 1 and months 1, 2 and 3, adjusted for age, visit and baseline nocturnal voids. A 33% responder was defined as a patient with a decrease of at least 33% in the mean number of nocturnal voids at each visit compared with baseline. Both studies met their co-primary endpoints. In CS41 analyses of desmopressin 75 microgram versus placebo were statistically significant, therefore testing of the desmopressin 50 microgram proceeded according to a

hierarchical step-down approach.[3,4] Results for the licensed doses of desmopressin only are presented in table 1, below.

Table 1: results of co-primary endpoints for studies CS40 and CS41 (licensed doses)

	Study CS40		**Study CS41**	
	desmopressin 25 microgram	**placebo**	**desmopressin 50 microgram**	**placebo**
N (FAS)	133	128	119	142
Mean number of nocturnal voids at baseline	2.84	2.88	2.88	2.90
Change from baseline in mean number of nocturnal voids	-1.46	-1.24	-1.25	-0.88
Treatment difference (95% CI), p-value	-0.22 (95% CI: -0.42 to -0.02), p=0.028		-0.37 (95% CI: -0.57 to -0.17), p=0.0003	
33% responder probability	0.76	0.64	0.67	0.50
Odds ratio (95% CI), p-value	1.85 (95% CI: 1.19 to 2.86), p=0.006		1.98 (95% CI: 1.32 to 2.96), p=0.0009	

FAS=full analysis set, CI=confidence interval

Results are available for the subgroups of patients aged ≥65 years (48% of study populations). In CS40, the adjusted mean change in nocturnal voids over three months was -1.31 for desmopressin and -0.96 for placebo, treatment difference -0.35 (95% CI: -0.65 to -0.05), and the proportion of 33% responders over three months was 0.71 for desmopressin and 0.55 for placebo, odds ratio 2.02 (95% CI: 1.11 to 3.69). In CS41, the adjusted mean change in nocturnal voids over three months was -1.06 for desmopressin 50 microgram and -0.63 for placebo, treatment difference -0.43 (95% CI: -0.72 to -0.14), and the proportion of 33% responders over three months was 0.58 for desmopressin 50 microgram and 0.40 for placebo, odds ratio 2.09 (95% CI: 1.19 to 3.69).[5]

Results of the secondary endpoints were supportive of the co-primary endpoints. Selected secondary endpoints are reported in table 2, below.

Table 2: results of secondary endpoints for studies CS40 and CS41 (licensed doses)

	Study CS40		**Study CS41**	
	desmopressin 25 microgram	**placebo**	**desmopressin 50 microgram**	**placebo**
N (FAS)	133	128	119	142
Mean time to first void at baseline	147 minutes	143 minutes	146 minutes	147 minutes
Change from baseline in mean time to first nocturnal void	155 minutes	106 minutes	112 minutes	73 minutes

Treatment difference (95% CI), p-value	49 minutes (95% CI: 16 to 82), p=0.003		39 minutes (95% CI: 11 to 67), p=0.0006.	
Mean nocturnal urine volume at baseline	627mL	607mL	607mL	620mL
Change from baseline in nocturnal urine volume	-235mL	-151mL	-209mL	-131mL
Treatment difference (95% CI), p-value	-84mL (95% CI: -139 to -28), p=0.003		-78mL (95% CI: -136 to -20), p=0.009	

FAS=full analysis set, CI=confidence interval

An exploratory assessment of quality of life included sleep quality ratings and the Nocturia Quality of Life (N-QoL). Sleep quality was rated on a scale of 1 (poor) to 10 (excellent) and a mean score over three successive mornings was obtained for three questions. The NQoL questionnaire included one statement on global QoL and 12 disease specific statements which were rated on a scale of 0 (lowest) to 4 (highest). Scores were transformed into a standardised score out of 100. In both studies, patients treated with desmopressin compared with placebo had their sleep quality improved, with most comparisons reaching statistical significance. Results of the NQoL questionnaire indicated statistically significant improvements in bother/concern and sleep/energy domains and total score in CS40, and in sleep/energy domain, global quality of life and total score in CS41.[3,4]

Study CS29 was a four-week study conducted in females and males and with similar inclusion criteria to the pivotal studies, in which patients were randomised to one of four doses of desmopressin (some not licensed and not discussed further) or placebo.[6] There were significant differences for desmopressin 50 micrograms versus placebo for the co-primary endpoint of change from baseline to week 4 in mean number of nocturnal voids. Long-term data are available from study CS31, an optional, open-label extension study to study CS29, where patients were treated for up to 96 weeks.[7] A total of 408 patients entered the long-term extension and 248 patients provided data on number of nocturnal voids after 52 weeks of treatment. At week 52, in the desmopressin 25 micrograms and 50 micrograms groups, respectively, the changes from baseline in mean number of nocturnal voids were -1.4 and -1.8, and the 33% responder probabilities were 0.74 and 0.73. Results are available (at week 52) for 40 women and 48 men treated with licensed desmopressin doses. In the desmopressin 25 microgram group, the change from baseline in mean number of nocturnal voids was -1.7 and the 33% responder probability was 0.88. In the desmopressin 50 microgram group, the change from baseline in mean number of nocturnal voids was -1.7 and the 33% responder probability was 0.63.

Summary of evidence on comparative safety

There are no comparative safety data other than versus placebo. In study CS40, adverse events considered by the investigator to be possibly/probably related to study medicine occurred in 19% (26/135) of desmopressin-treated patients and 12% (15/126) of placebo-treated patients, and those leading to treatment discontinuation occurred in 2.2% (3/135) and 0% of patients respectively. There was one severe and no serious adverse events in the desmopressin group compared with three severe and two serious adverse events in the placebo group.[3]

In study CS41, adverse events considered by the investigator to be possibly/probably related to study medicine occurred in 19% (23/119) of desmopressin-treated patients and 15% (22/143) of placebo-treated patients, and those leading to treatment discontinuation occurred in 3.4% (4/119) and 2.8% (4/143) of patients respectively. There were two severe and four serious adverse events in the desmopressin group 50 microgram compared with two severe and one serious adverse event in the placebo group.[4]

Serum sodium was measured during screening and at all study visits thereafter; any patient with a serum sodium ≤130mmol/L underwent investigation and those with a serum sodium ≤125mmol/L were immediately withdrawn. In study CS40, in the desmopressin and placebo groups respectively, the proportion of patients with serum sodium of 126 to 129mmol/L was 2.2% (3/135) versus no patients. Serum sodium returned to >130mmol/L within two to four days without the need to discontinue treatment in all three patients (two of whom had serum sodium less than 135mmol/L at baseline). In study CS41, no patients had serum sodium of 126 to 129mmol/L. Two patients in the desmopressin 50 microgram group had serum sodium ≤125mmol/L; one patient was taking concomitant medicines (enalapril and lovastatin) which may have contributed to the hyponatraemia. Following treatment discontinuation in these patients serum sodium returned to values >130mmol/L.[3,4,8,9]

In the longer term study, desmopressin was well tolerated with similar frequency and type of adverse events to those reported in shorter term studies.[7]

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

There are no other treatments licensed for symptomatic treatment of nocturia due to idiopathic nocturnal polyuria in adults aged at least 65 years. Current strategies include lifestyle or behavioural modifications, and medicines such as alpha-blockers, antimuscarinics and antidiuretics, and desmopressin are likely to be used in addition to these. Off-label use of other formulations/strengths of desmopressin has been noted.[10]

The submitting company has requested that SMC considers desmopressin when used in patients aged 65 years and over.

Two phase III, placebo-controlled studies (CS40 in females and CS41 in males) demonstrated that desmopressin at licensed doses over three months significantly reduced the mean number of nocturnal voids and resulted in higher proportions of 33% responders compared with placebo. A longitudinal analysis was used for the co-primary endpoints as data from the previous CS29

study indicated some variability at each individual time point. It was considered that an average response over a longer treatment period might be more representative of the clinical benefit. Subgroup analyses of the pivotal studies provide evidence of efficacy in patients aged ≥65 years, where similar results to the overall populations were observed. However, there are no efficacy data specifically in patients with idiopathic nocturnal polyuria and aged ≥65 years, the positioning within the licensed indication proposed by the company. Nocturnal polyuria was not a specific inclusion criterion in the pivotal studies. However, at baseline, 89% of women and 87% of men met the definition of nocturnal polyuria (nocturnal urine output 33% of 24-hour output) and patients with potentially treatable medical underlying causes for nocturia were excluded from the studies. Furthermore, results of the co-primary endpoints in the subgroups of patients with nocturnal polyuria were the same as in the total study populations.[3-5]

In the overall populations of the pivotal studies, treatment with desmopressin compared with placebo improved sleep quality and quality of life, assessed using the NQoL questionnaire (where a treatment difference at three months of approximately five points has been suggested as being clinically meaningful). High placebo responses were observed in these studies; however, all patients were instructed on lifestyle and behavioural modifications. This may have contributed to the placebo response, in addition to completion of diaries which may have raised awareness of these issues. The authors of the study publications noted that high placebo responses have previously been seen in urological studies (e.g. over active bladder and benign prostatic hyperplasia).[3-5]

There are no comparative data versus desmopressin preparations used off-label. Furthermore, there are limited long-term data for desmopressin at licensed doses. In 40 females treated with desmopressin 25 microgram and 48 males treated with desmopressin 50 micrograms, the change in mean number of nocturnal voids from baseline to week 52 was -1.7.[3,4,7]

Data on falls or fractures were not collected in the pivotal studies. However, the submitting company provided some observational data on nocturia and the increase in the risk of fall-related fractures in elderly patients. Clinical experts consulted by SMC were asked to comment on this potential relationship. Some considered the association to be plausible but acknowledged that the relationship has not been shown to be causative, and noted that other factors such as reduced balance, impaired muscle function and hyponatraemia may also be important. Treatment with desmopressin may cause hyponatraemia and dizziness.[1,2]

For entry into the pivotal studies, patients were required to have a serum sodium ≥135mmol/L. Hyponatraemia occurred in a higher proportion of desmopressin than placebo treated patients in both studies.[3,4] The summary of product characteristics for desmopressin advises that, in patients aged at least 65 years, serum sodium should be within the normal range before initiating treatment, and monitored in the first week and at one month of treatment. Desmopressin should be discontinued if the serum sodium level falls below the lower limit of the normal range. Use of desmopressin 50 micrograms in females is not recommended due to increased risk of hyponatraemia at this dose compared to males.[1,2]

Some clinical experts consulted by SMC noted potential issues in terms of the diagnosis of idiopathic nocturnal polyuria. They considered that the introduction of desmopressin may have service implications in terms of its safe and effective use as well as the monitoring requirements for serum sodium.

Summary of comparative health economic evidence

A cost-utility analysis was presented comparing desmopressin, at variable gender- specific doses, to best-supportive care (BSC) in a population of patients aged 65 years and over with nocturia due to idiopathic nocturnal polyuria. The time horizon used was a lifetime horizon of 35 years.

A cohort Markov model was used to synthesise evidence and extrapolate beyond the study period. The model used 4 health states based on the number of times the patient voided urine during the night: <2 voids (no nocturia/remission), 2-3 voids (moderate nocturia), ≥4 voids (severe nocturia) and death. Fractures were simulated through the use of modified health states for the cycle in which the fracture occurred and the following three cycles. Additional costs and utility decrements are applied to the states in these cycles. Fractures were divided into 6 groups (hip, wrist, humerus (diaphyseal), humerus (proximal), femur, tibia and forearm) and transition probabilities were calculated for each fracture type separately.

Key clinical evidence was taken from the CS40 (females only) and CS41 (males only) pivotal studies. Results from baseline and at 3 month follow-up in the subgroup of patients aged 65 and over were used to populate the economic model. The co-primary endpoint of change from baseline in mean number of nocturnal voids during 3 months of treatment, used in both studies, was the key outcome. CS41 was used for male patients and CS40 was used for female patients for estimating both the initial distribution of patients into nocturia states and transition probabilities for the first three months for the desmopressin group. The transition probabilities for the first three months for the BSC group were based on the CS40 and CS41 placebo group results in the base case analysis.

Transition probabilities for all cycles after the first three months were based on the assumption that the condition is completely stable ie no transitions between states occur after three months. In the BSC group, it is assumed that patients in the moderate and severe nocturia states remain in these states indefinitely. However, patients in the remission state in the BSC group had a non-zero probability (approximately 7% per cycle) of moving to the moderate nocturia state. This was justified by the assumption that improvements in nocturia in the placebo groups in the pivotal studies represent a pure placebo effect ie improvements were not due to a condition with a fluctuating natural history or other aspects of care. This assumption results in almost all patients in the BSC group moving from remission back to moderate nocturia over the lifetime horizon of the model.

The relative risk of fracture in each of the nocturia states was calculated based on estimates from three survey/observational studies identified by the submitting company from a non-systematic literature search. The mean relative risk across the three studies was applied to calculate increased fracture risk.

No generic health-related quality of life (QoL) data were recorded in the key CS40 and CS41 studies. The CS29 study provided SF-12 data that were converted to utilities via a mapping algorithm to the SF-6D utility weights. Data were age and gender stratified to produce utility weights in three age groups for each gender. Utility decrements were applied for each fracture type. These were sourced from previously published studies. The source studies used the EQ-5D survey instrument in populations similar to but not identical to the population considered in the submission.

Medicines acquisition and monitoring costs were included. Serum sodium monitoring was also assumed before treatment, in the first week and after one month. Monitoring resource use included a nurse visit and a standard blood test. Adverse event costs were included for hyponatraemia only. Each incidence of hyponatraemia was assumed to lead to resource use of two GP visits, two blood test and two urine tests only. The costs associated with fractures were estimated from various published sources.

The incremental cost-effectiveness ratio (ICER) in the base case was £7,168. This resulted from a gain of 0.223 quality-adjusted life-years (QALYs) and an additional cost of £1,600 per patient. Excluding any effect on fracture risk, the ICER was increased to £11,808 (incremental QALYs: 0.204 incremental costs: £2,412).

A one-way sensitivity analysis was performed, including all key model parameters. The key drivers of cost-effectiveness results were the discount rate (outcomes and costs), the relative risk for fractures caused by nocturia (>2 voids), the utility weights applied to nocturia states and the time horizon, but in all analyses the ICER remained <£10k per QALY.

A number of other scenario analysis were performed. This included a 'Real world scenario' that assumed that all improvements in nocturia that were observed in the placebo control groups in the pivotal studies were due to a placebo effect. The BSC scenario was changed so that patients nocturia states did not improve from baseline values by setting the transition probabilities to zero. Sensitivity to fracture risk estimate was explored by using relative risk of fracture taken from each of the three individual sources. Sensitivity to shortened time horizons was also explored and highlighted the sensitivity of the model to the assumption made in extrapolating beyond the period of the key studies. Results are shown below:

Scenario	Incremental Costs (£)	Incremental QALYs	ICER (£)
'Real world'	1,410	0.302	4,673
Fracture risk sources:			
Asplund 2006	1,388	0.229	6,061
Parsons et al 2009	2,251	0.206	10,936
Rafiq et al 2014	1,165	0.235	4,961
Short time horizons:			
5 years	792	0.057	13,964
1 year	208	0.007	28,233
3 months	81	0.001	58,504

The main weaknesses of the analysis are:

- While it is noted that extension study data provide some support for continuing benefit of treatment with desmopressin beyond 3 months, the assumption of patients remaining in the same nocturia states over the lifetime of the model is associated with uncertainty. The company provided additional analysis at a time horizon of 2 years (similar to the duration of available extension data) which gave an ICER of £20,871.
- The assumption of stability in the non-remission states and a transition from remission to moderate nocturia for the BSC group were also not well supported by the presented clinical evidence. This pattern of transition probabilities depends on the assumption that the improvements in nocturia observed in CS40 and CS41 placebo groups are strictly due to a

placebo effect. Improvements may also be due to natural fluctuations in the condition or other aspects of care. If this assumption of a true placebo effect is not met then the estimated transition probabilities may not be appropriate and the difference in effectiveness between BSC and desmopressin in the long-term would be greatly reduced.

- The weaknesses described above lead to an overall weakness in the extrapolation outcomes over a lifetime horizon. The economic model may not accurately reflect the natural history of the condition and may lead to major bias in favour of desmopressin. As analysis with alternative assumptions regarding the long-term stability of the condition was not provided, it is difficult to assess the cost-effectiveness under alternative assumptions. Further analysis was provided upon request to address the issue of assuming a pure placebo effect. This scenario analysis assumed that patients from the BSC/placebo group in remission at 3 months were equally stable as desmopressin patients in the base case analysis ie all patients in remission at 3 months remain in remission thereafter in both treatment groups. This resulted in higher ICERs of £24,064 (0.088 additional QALYs and £2,111 of additional costs) when fractures were included, and £30,023 (0.08 QALYs gained and £2,412 of additional costs) when fractures were excluded.
- An important assumption in the model is that the relative risk of fracture associated with nocturia in observational studies is a causal effect. Responses from SMC clinical experts provided mixed support for the assumption that there could be an impact on fractures, and noted the estimated association may be biased by confounding factors that are associated with both nocturia and other symptoms that increase the risk of falls and fractures. As such, the committee felt that the inclusion of this aspect into the base case was uncertain. There were also additional concerns with the methods that had been used to estimate the relative fracture risks from the literature and also the calculation of the associated costs.
- No health-related quality of life data were available from the pivotal studies. Instead data from a earlier variable dose study (CS29) and extension were used. Utility weights were reported to increase with age, which is the opposite to what is found in most studies. Patients in this study are less representative of the population considered in the submission compared to those included in the pivotal studies; this increases uncertainty around the ICER.

Given the weaknesses noted above in the extrapolation beyond the trial period and the resulting potential for major bias in favour of desmopressin, the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

There are no relevant up-to-date guidelines relating to the use of desmopressin lyophilisate (Noqdirna®).

The European Association of Urology published Guidelines on the treatment of non-neurogenic male lower urinary tract symptoms (LUTS), in 2016. This recommends that: "*Desmopressin may be prescribed to decrease nocturia due to nocturnal polyuria in men under the age of 65. Screening for hyponatremia must be undertaken at baseline, during dose titration and during treatment*."[10]

The National Institute for Health and Care Excellence (NICE) published clinical guideline (CG) 171, Urinary incontinence in women: management, in November 2015. This states: "*The use of desmopressin may be considered specifically to reduce nocturia in women with UI or OAB who find it a troublesome symptom. Use particular caution in women with cystic fibrosis and avoid in those over 65 years with cardiovascular disease or hypertension*".[14]

NICE CG97 Lower urinary tract symptoms in men: management was published in June 2015. This states: "*Consider offering oral desmopressin to men with nocturnal polyuria if other medical causes have been excluded and they have not benefited from other treatments. Measure serum sodium 3 days after the first dose. If serum sodium is reduced to below the normal range, stop desmopressin treatment".*[15]

All guidelines predate the licensing of desmopressin (Noqdirna®) for nocturia due to idiopathic nocturnal polyuria.

Additional information: comparators

There are no other licensed treatments for this indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Desmopressin oral lyophilisate	**25 micrograms (females) or 50 micrograms (males) sublingually daily, one hour before bedtime**	**184**

Cost from DM&D on 9 November 2016.

Additional information: budget impact

The submitting company estimated there would be 31,305 patients eligible for treatment with desmopresin oral lyophilisate in year 1, rising to 31,687 patients in year 5. The estimated uptake rate was 0.1% in year 1 (38 patients), rising to 11.8% in year 5 (3,732 patients), with a discontinuation rate of 2.4% applied in year 1 and 0.5% in year 5.

The gross impact on the medicines budget was estimated to be £7k in year 1, rising to £688k in year 5. As no medicines were assumed to be displaced, the net medicines budget impact is equivalent to the gross impact.

References

The undernoted references were supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 15 December 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including

via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.
This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.