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All Wales Therapeutics & Toxicology Centre
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AWMSG SECRETARIAT ASSESSMENT REPORT

Desmopressin actetate (Noqdirna®)
25 microgram and 50 microgram oral lyophilisate

Reference number: 3282

FULL SUBMISSION

PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

Please direct any queries to AWTTC:

All Wales Therapeutics & Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

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AWMSG Secretariat Assessment Report
Desmopressin acetate (Noqdirna®) 25 microgram and 50 microgram oral lyophilisate

This assessment report is based on evidence submitted by Ferring Pharmaceuticals Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Desmopressin acetate (Noqdirna®) for the treatment of nocturia due to idiopathic nocturnal polyuria in adults[2,3].
Dosing	50 micrograms for men and 25 micrograms for women daily, administered sublingually without water 1 hour before bedtime. If higher doses are required for patients aged under 65 years because of an insufficient response, other desmopressin acetate oral lyophilisate products should be used. Elderly patients are at increased risk of developing hyponatraemia with desmopressin acetate treatment and doses above 25 micrograms for women and 50 micrograms for men should not be used. Refer to the Summary of Product Characteristics for further information[2,3]. Ferring Pharmaceuticals Ltd proposes a two-year 'stop and review' rule under which after two years patients would stop treatment for one week and only restart treatment if their symptoms worsened[1].
Marketing authorisation date	18 May 2016[2,3]

2.0 DECISION CONTEXT

2.1 Background

The International Continence Society defines nocturnal polyuria as the "excessive production of urine during the sleep or night period"[4]. The condition is diagnosed in people aged > 65 years when nocturnal urine volume exceeds 33% of the total 24-hour urine volume[4]. In Wales in 2015–2016, there were 609 primary diagnoses of polyuria, over half of which (339 cases) were in people aged over 60 years[5].

The prevalence of nocturia, defined as waking at night 1 or more times to void, increases with age in both men and women, and it is estimated that around 70% of people aged 70 years and older are affected by it[6]. Nocturia affects a person's quality of life, mainly because of disturbed sleep, which can lead to daytime fatigue, poor concentration and impaired memory[7]. Chronically impaired sleep has also been associated with increased mortality and a 25% increased risk of falls in older people[7].

Treatment of nocturia depends on identifying the underlying cause[7]. If there is no specific cause identified (idiopathic) then advice on behavioural and lifestyle changes may be offered first[7,8]. Medicines that may be used to reduce nocturia include loop diuretics, antimuscarinic agents and antidiuretics[7]. The company claims that treatments for overactive bladder or benign prostatic hyperplasia will not reduce the number of

nocturnal voids for people with nocturnal polyuria because these treatments do not address the underlying cause[1].

Desmopressin acetate is an analogue of the antidiuretic hormone arginine vasopressin[2,3]. It binds to the V2 receptors in the renal collecting tubules of the kidneys, causing reabsorption of water. This reabsorption decreases the production of urine[2,3]. Desmopressin acetate has been used for over 30 years to treat diabetes insipidus and primary nocturnal enuresis and it is approved in most of Europe to treat nocturia due to nocturnal polyuria in adults[9]. The oral lyophilisate formulation of desmopressin acetate (Noqdirna®) for sublingual use contains desmopressin acetate equivalent to 25 or 50 micrograms of desmopressin acetate[2,3]. Company-sought clinical expert opinion has confirmed that other formulations of desmopressin acetate are sometimes given off-label to treat nocturnal polyuria[1]. However, these are not recommended in people aged > 65 years due to the increased risk of developing hyponatraemia[1]. Noqdirna® allows the sublingual administration of lower doses than previously licensed desmopressin acetate formulations, and therefore may be more suitable for treating this condition in adults aged 65 years and older[2,3].

The company's submission therefore focuses on treating nocturia due to idiopathic nocturnal polyuria in people aged over 65, for whom treatment options are currently limited[1].

2.2 Comparators

The company did not highlight a specific comparator in its submission[1]. In the company's economic evaluation, low-dose Noqdirna® is compared with:

- Desmopressin acetate nasal spray
- desmopressin acetate oral tablets (Desmotabs®)
- no treatment (lifestyle advice only)[1].

2.3 Guidance and related advice

- European Association of Urology (2015) Guidelines on the management of non-neurogenic male lower urinary tract symptoms (LUTS), including benign prostatic obstruction (BPO)[9]
- NICE guideline CG171 (2013) Urinary incontinence in women: management[10]
- NICE advice ESUOM10 (2013) Nocturia and nocturnal polyuria in men with lower urinary tract symptoms: oral desmopressin[11]
- NICE guideline CG97 (2010) Lower urinary tract symptoms in men: management[12]

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company's submission includes data from three phase III randomised, double-blind studies that assessed the safety and efficacy of Noqdirna® compared with placebo in treating nocturia[1]. One study (CS29) assessed a range of doses in a mixed population and had an open-label extension (CS31). Based on the results of study CS29, two other studies (CS40 and CS41) evaluated gender-specific doses. There are gender differences in the clinical efficacy and safety of Noqdirna®, with a dose response plateau at 25 micrograms in women whereas a dose of 50 micrograms shows efficacy in men. Doses of 50 micrograms in women were associated with a five-fold increase in risk of hyponatraemia. Data are presented for the licensed doses of Noqdirna® only (25 and 50 micrograms)[1].

The studies were conducted in the USA and Canada[13-16]. Inclusion criteria were the same for all three studies and included: age > 18 years; nocturia (defined as two or more voids per night); serum sodium ≥ 135 mmol/litre; normal serum creatinine levels; and a glomerular filtration rate > 60 ml/min. People with potentially treatable causes of

nocturia were excluded, and also those with urinary retention and/or post-void residual volume > 150 ml, or history of urologic malignancies, neurogenic detrusor activity or current genitourinary tract pathology that could interfere with voiding. All patients were asked to empty their bladders before bed, to drink only if thirsty, and the drinking of diuretic fluids, such as caffeine or alcohol, in the evenings was discouraged[13-16].

Each study had two co-primary endpoints: change from baseline in the mean number of nocturnal voids and the 33% responder status during the three months of treatment[13-16]. A 33% responder was defined as a patient with a decrease of at least 33% in the mean number of nocturnal voids across three nights preceding a planned visit compared with baseline[1]. Secondary endpoints included: change from baseline at 3 months in mean number of nocturnal voids; change in initial period of undisturbed sleep; change in mean nocturnal urine volume; and change in nocturia quality of life questionnaire (N-QoL) scores[13-16].

3.1 Studies CS29 and CS31

Study CS29 was a four-week study that was powered to demonstrate superiority of Noqdirna® to placebo in treating nocturia[13]. A total of 799 people were randomised to receive either: placebo, or 10, 25, 50 or 100 micrograms of Noqdirna® given one hour before bedtime every day for 28 days. Randomisation was stratified by age (< 65 or ≥ 65 years) and the presence of nocturnal polyuria (defined as night-time urine volume/24-hour urine volume ≥ 33%)[13].

The intent-to-treat population (n = 757) included all randomised patients who received ≥ one dose of Noqdirna® or placebo and gave more than one post-baseline primary efficacy measure; of these, 710 patients completed the study[13]. The mean age of patients was around 62 years in the placebo, 25 and 50 microgram groups; 91% had nocturnal polyuria and the baseline number of voids ranged from 3.27 to 3.39[13].

Results showed that both primary endpoints were met (Table 1)[13]. Noqdirna® reduced the mean number of nocturnal voids from baseline in both male and female patients[13]. The percentages of patients who achieved > 33% reduction from baseline in the mean number of nocturnal voids over the study period were 62% in women treated with 25 micrograms Noqdirna® and 48% in men treated with 50 micrograms.

Table 1. Results from study CS29: changes from baseline[13]

	Noqdirna® 25 micrograms		Noqdirna® 50 micrograms		Placebo	
Co-primary endpoints	**n**	**mean**	**n**	**mean**	**n**	**mean**
Number of nocturnal voids (n)						
All	152	–1.0 (SD 1.13; p = 0.31)	148	–1.18 (SD 1.19;p = 0.02*)	156	–0.86 (SD 1.05)
Men	87	–0.83 (SD 1.15; p = 0.6)	77	–1.13 (SD 1.3; p = 0.4)	90	–0.84 (SD 1.09)
Women	65	–1.22 (SD 1.06; p = 0.02*)	71	–1.23 (SD 1.06; p = 0.009*)	66	–0.88 (SD 1.01)
33% responder rate, n (%)						
All	152	76 (50)	148	79 (53)	156	73 (47)
Men	87	36 (41)	77	37 (48)	90	45 (50)
Women	65	40 (62)	71	42 (59)	66	28 (42)
Secondary endpoints	**n**	**mean**	**n**	**mean**	**n**	**mean**
Initial period of undisturbed sleep (minutes)						
All	121	83 (SD 106; p = 0.001*)	123	85 (SD 109; p = 0.0008*)	126	39 (SD 89)
Men	70	61 (SD 90; p = 0.18)	62	72 (SD 90; p = 0.07)	77	40 (SD 86)
Women	51	113 (SD 118' p=0.0012*)	61	98 (SD 125; p = 0.0048*)	49	37 (SD 94)
Urinary volume (nocturnal; ml)						
All	144	–224 (SD 264; p = 0.0001*)	138	–272 (SD 296; p < 0.0001*)	140	–109 (SD –109)
Men	87	–163 (SD 238; p = 0.15)	77	–286 (SD 309; p = 0.0029*)	90	–125 (SD 219)
Women	65	–307 (SD 276; p < 0.00001*)	71	–257 (SD 282; p < 0.0001*)	66	–86 (SD 278)

* Statistically significant compared with placebo (p < 0.05)
SD: standard deviation

A supplemental analysis of data by gender showed that Noqdirna® had a lower minimal effective dose in women than in men[1]. In women, doses of 25 micrograms of Noqdirna® upwards were statistically significantly superior to placebo for both primary efficacy endpoints; whereas in men a statistically significant reduction was only observed at the 100 microgram dose (unlicensed dose)[13]. Statistically significant decreases in nocturnal urine volume were seen at doses of 25 micrograms of Noqdirna® upwards in women and at doses of 50 micrograms upwards in men, compared with placebo treatment. The initial period of undisturbed sleep was statistically significantly increased at doses of 25 micrograms of Noqdirna® upwards in women and at doses of 100 micrograms in men, compared with placebo[13].

An extension study (CS31) evaluated the long-term safety and durability of Noqdirna® efficacy over 52 weeks in 408 patients who completed study CS29[14]. Patients who received placebo in study CS29 were re-randomised to receive either 25, 50 or 100 micrograms of Noqdirna® or placebo. Data were available from 248 patients after 52 weeks of treatment. The results confirmed that efficacy was maintained after longer-term treatment: the mean decrease in the number of nocturnal voids was increased over time and reached 1.4 voids in the 25 microgram Noqdirna® group and 1.8 voids in the 50 microgram group. At 52 weeks the initial period of undisturbed sleep increased by approximately 2 hours[14].

Longer-term data up to 92 weeks were included in the company submission, showing similar trends to the published data providing evidence for the efficacy of Noqdirna® up to 52 weeks[1].

3.2 Studies CS40 and CS41

These studies evaluated three months of Noqdirna® treatment[15,16]. Study CS40 in 268 women compared a dose of 25 micrograms of Noqdirna® with placebo[16], and study CS41 in 395 men investigated doses of 50 and 75 micrograms of Noqdirna® compared with placebo[15]. Clinical benefit was assessed using the N-QoL and the Work Productivity and Activity questionnaires; participants also self-rated sleep quality[15,16].

In study CS40, the final analysis set (those who had at least one efficacy assessment) consisted of 261 women: 128 who received placebo and 133 who received Noqdirna®[16]. In CS41, the final analysis set consisted of 385 men: of whom 142 received placebo, 119 received Noqdirna® 50 micrograms and 124 received Noqdirna® 75 micrograms[15]. The mean age of patients ranged from 59.5 to 60.8 years in both studies; in CS41 48% of men were over 65 years in each study arm and in CS40 47% of women who received Noqdirna® and 49% of those in the placebo group were over 65 years[15,16].

Both co-primary endpoints were met in both studies: Noqdirna® showed statistically significant superiority to placebo (Table 2)[15,16]. The treatment difference was similar for patients aged 65 years and older and those aged less than 65 years[15,16].

Table 2. Studies CS40 and CS41: results for co-primary endpoints[1,15,16]

Change from baseline in mean number of nocturnal voids over the duration of treatment				
Study CS40 (women)[16]	**Dose**	**Change in mean number of nocturnal voids**	**Treatment difference (95% CI)**	**P value**
All ages	Placebo	–1.24	–0.22 (–0.42 to –0.02)	0.028*
	25 micrograms Noqdirna®	–1.46		
Age ≥ 65 years†	Placebo	–0.96	–0.35	0.022*
	25 micrograms Noqdirna®	–1.31		
Study CS41 (men)[15]	**Dose**	**Change in mean number of nocturnal voids**	**Treatment difference (95% CI)**	**P value**
All ages	Placebo	–0.88	–0.37 (–0.37 to –0.17)	0.0003*
	50 micrograms Noqdirna®	–1.25		
Age ≥ 65 years†	Placebo	–0.63	–0.43	0.004*
	50 micrograms Noqdirna®	–1.06		
Proportion of people with a decrease of at least 33% in the mean number of nocturnal voids				
Study CS40 (women)[16]	**Dose**	**33% responder probability**	**Odds ratio (95% CI)**	**P value**
All ages	Placebo	0.64	1.85 (1.19 to 2.86)	0.006*
	25 micrograms Noqdirna®	0.76		
Age ≥ 65 years†	Placebo	0.55	2.02	0.0221*
	25 micrograms Noqdirna®	0.71		
Study CS41 (men)[15]	**Dose**	**33% responder probability**	**Odds ratio (95% CI)**	**P value**
All ages	Placebo	0.50	1.98 (1.32 to 2.96)	0.0009*
	50 micrograms Noqdirna®	0.67		
Age ≥ 65 years†	Placebo	0.40	2.09	0.0106*
	50 micrograms Noqdirna®	0.58		

* Statistically significant difference versus placebo; $p \leq 0.05$
† Data from Form B
CI: confidence interval
NB repeated measures ANCOVA of change from baseline at week 1 and months 1, 2 and 3, adjusted for age (< 65; ≥ 65 years), visit and baseline nocturnal voids

For the secondary endpoints, significant differences were seen between Noqdirna® treatment and placebo treatment after 3 months of treatment in men[15]. In women, significant differences between Noqdirna® treatment and placebo treatment were seen at 3 months only for change in mean number of nocturnal voids, mean time to first void and mean nocturnal urine volume[16]. However, the 33% responder rate did not reach statistical significance[16].

Self-reported sleep quality improved after Noqdirna® treatment in both studies[1]. [Commercial in confidence text removed]

Health-related quality of life, measured using N-QoL, showed statistically significant improvement with Noqdirna® treatment after 3 months for women (confidence interval [CI]: 0.76 to 9.92; p = 0.0226) and men (CI: 0.24 to 8.74; p = 0.0385)[1]. In women (CS40), two out of the three sleep quality ratings (p = 0.04 and 0.03), and the activity impairment questionnaire percentages (p = 0.03) were statistically significantly

improved[16]. In men (CS41) who received 50 micrograms, Noqdirna® also showed improvements in sleep quality ratings[15].

3.3 Comparative safety

All safety data for Noqdirna® are compared with placebo; there are no data available on its safety versus comparator treatments[1].

In the clinical studies Noqdirna® was well tolerated and safety data were consistent with those from previous studies of desmopressin acetate solid tablets[13]. Rates of adverse events were low in all studies[1]. Treatment-emergent adverse events with an incidence of 5% or more included dry mouth and headache in men[15], and urinary tract infection, headache and upper respiratory tract infection in women[16]. Rates of discontinuation of Noqdirna® were higher in people aged over 65 years, and the rates of adverse drug reactions were higher in women aged over 65 years[1]. The frequency and type of adverse events in the long-term open-label extension study (CS31) were similar to those in the four-week study CS29[14]. Noqdirna® was well tolerated during longer-term exposure[14].

Hyponatraemia is a known safety issue associated with desmopressin acetate treatment[13]. A systematic review conducted in 2013 identified hyponatraemia as a common adverse effect, with a relative risk of 5.1 (95% CI 3.0 to 8.8)[17]. In the clinical studies most cases of hyponatraemia occurred in people aged over 65 years[1]. Most cases were mild to moderate and all resolved after stopping Noqdirna® treatment[1]. Severe hyponatraemia was not seen in any women in study CS40; in study CS41 severe hyponatraemia was seen [commercial in confidence text removed], serum sodium levels returned to > 130 mmol/litre after stopping treatment[15]. In study CS29, hyponatraemia was only reported in people who received doses of Noqdirna® that were higher than the recommended gender-specific doses[1]. The Summary of Product Characteristics (SPC) recommends that people aged 65 and older should have their serum sodium levels monitored before starting treatment, during the first week of treatment (4–8 days) and one month after starting treatment[2,3]. Noqdirna® is contraindicated in people with a known history of hyponatraemia[2,3].

3.4 AWTTC critique

- The company's submission focuses on using Noqdirna® to treat nocturia in people aged 65 years and older[1]. At the time of writing, there is no alternative licensed medicine for treating nocturia caused by idiopathic nocturnal polyuria in people aged 65 and over, so there exists an unmet need in this population. For all clinical studies included in the company's submission more patients were aged under 65 years; 47–49% of patients were aged over 65 years[13,15,16]. However, data from sub-group analyses in patients aged 65 years and older show similar results to the whole study populations.
- Noqdirna® has been shown to reverse nocturia in a significant proportion of patients by reducing the average number of voids below 2 per night[1], which is considered by AWTTC-sought clinical expert opinion to be acceptable as a threshold for clinical significance.
- Clinical studies show that Noqdirna® is effective in reducing the number of night-time voids, increasing the time to first void, and indicate an improvement in quality of life. The company also suggests that reducing the number of times that an older person has to get up during the night to void may lower their risk of falls or fractures[1]. Falls and fractures were not investigated in the pivotal studies.
- There are no comparative safety data. However, the safety data from the clinical studies are similar to those seen in clinical practice with other formulations of desmopressin acetate[13].
- A high placebo response was observed in the studies[15], which is noted as a common feature of clinical studies of pharmacological treatments for lower

urinary tract symptoms[18]. (See limitations of economic analysis [section 4.1.3] for further information).

- Company-sought clinicians report using other desmopressin acetate formulations, such as nasal spray, off-label to treat nocturia in older people. However, these formulations are only available in higher doses at which older people are more likely to develop hyponatraemia.
- People aged 65 years and older who are treated with Noqdirna® should have additional monitoring, as stated in the Noqdirna® SPC[2,3]. AWTTC-sought clinical expert opinion in Wales have confirmed that additional monitoring is already undertaken when other desmopressin acetate formulations are given off-label to people aged 65 years and older.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission includes a cost-utility analysis of sublingual low-dose Noqdirna® 25 micrograms and 50 micrograms compared with standard of care (no treatment) for symptomatic nocturia due to idiopathic nocturnal polyuria in adults aged 65 years and older[1]. It also includes a cost-minimisation analysis comparing Noqdirna® with off-label use of nasal and oral preparations of desmopressin acetate.

A four-state Markov model with an NHS perspective assesses the cost-effectiveness of Noqdirna® compared with no treatment in 3-month cycles[1]. Patients enter the model at age 65 years in either the moderate nocturia state (2 or 3 voids per night) or the severe nocturia state (4 or more voids per night) based on gender-specific distributions from studies CS40 and CS41[15,16]. Women in the intervention group (54%) receive 25 micrograms of Noqdirna®; men (46%) receive a dose of 50 micrograms. Based on data from the studies, the number of voids can remain constant, increase or decrease. If the number of voids is reduced to < 2, patients enter the remission state. Transition probabilities for patients in the Noqdirna® arm were taken from the treatment arm of studies CS29[13], CS40[16] and CS41[15] for the first cycle and from the extension study CS31 thereafter[14]. Transition probabilities for patients in the no treatment arm were taken from the placebo arms of studies CS40 and CS41[15,16] for the first cycle and from natural history data[19] for all subsequent cycles. Fractures can occur in any alive health state but their probability increases with increasing number of voids. The probability of fractures is the average of risk ratios reported in several relevant publications[20-24] identified in a systematic review by the company. The probability of fracture in the remission state is that of the general population. Patients who experience hyponatraemia (serum sodium levels < 135 mmol/l) in the first three months discontinue treatment. Based on the "stop and review" rule proposed by the company, after the first 2 years of treatment 11.6% of men[19] and 18.9% of women are assumed to discontinue treatment due to resolution of nocturia. This discontinuation pattern continues every cycle thereafter. Patients can die from any cause and move to the dead state based on standard life tables[25]. Furthermore, a 7% higher mortality rate[26] is applied for patients who have a fall-related hip fracture in the cycle where the fracture occurs. The model assumes a 19–year time horizon and a 3.5% discounting rate is applied to both costs and benefits. The model calculates cost-effectiveness based on cost per quality-adjusted life year (QALY) gained[1].

Costs considered in the model include: treatment costs; cost of sodium level monitoring; costs associated with hyponatraemia; and healthcare cost of fractures including hospitalisation, GP visits, assessment, home care and nursing care. Costs of treatment are taken from the British National Formulary[27] and monitoring costs are derived from published unit costs[28,29]. Published data are used to estimate the costs of fractures of the hip[30], wrist[31] as well as humerus, tibia, femur and forearm[32]. Costs of

hyponatraemia are assumed to consist of two GP visits[28], two blood tests and two urine tests[29]. Utility values are calculated by applying a decrement of 5.1% to age-specific utilities for the general population for patients who had 2 to < 4 voids and 8.0% for patients who had ≥ 4 voids based on nocturia utilities reported by an observational European survey[33]. Separate disutility multipliers based on published data[34-36] are applied in the first and subsequent years after fracture to account for immediate and long-term consequences of fractures on patients' health-related quality of life. In the absence of published data, the disutility of hyponatraemia was assumed to be 0.05 for 10 days, based on the time taken for patients to regain normal serum sodium levels in studies CS40[16] and CS41[15].

Parameter uncertainty is assessed by extensive deterministic sensitivity analysis, probabilistic sensitivity analysis and scenario analyses.

For the cost-minimisation analysis, the cost of off-label desmopressin acetate formulations for one year is calculated using published unit costs weighted according to market share[37]. This is then compared with the cost of Noqdirna®. All other parameters are assumed equal.

4.1.2 Results

The results of the company's base case suggest that treatment with Noqdirna® is associated with 9.37 discounted QALYs compared with 9.19 discounted QALYs in the standard of care arm, at an incremental cost of £1,278 per patient. This gives an incremental cost-effectiveness ratio (ICER) of £6,989 per QALY gained. Furthermore, the model estimates that the incidence of fractures is reduced by 9–10% in the Noqdirna® arm.

Noqdirna® is less costly than off-label desmopressin acetate with an annual cost saving of £157.23 per patient.

Table 3. Results of the base case analysis

	Noqdirna®	SOC (no treatment)	Difference
Cost-utility analysis			
Total cost per patient	£4,660	£3,383	£1,278
Treatment	£1,543	£0	£1,543
Fractures	£3,081	£3,383	–£302
Monitoring	£32	£0	£32
Adverse events	£4	£0	£4
Total QALYs per patient	9.373	9.191	0.183
ICER (£/QALY gained)	£6,989		
	Noqdirna®	**Off-label desmopressin acetate**	**Difference**
Cost-minimisation analysis			
Annual cost per patient	£184.45	£341.68	–£157.23
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SOC: standard of care			

Table 4 summarises the scenarios provided by the company to address uncertainty around the key input parameters of the cost-utility analysis. Several scenario analyses were tested using alternative data sources. The ICERs using these alternatives range from £5,963 to £9,087 per QALY gained. The company submission does not include scenario analyses of the cost-minimisation analysis.

Table 4. Results of the scenario analyses

Scenarios	ICER	Plausibility
Scenario 1: Real-world scenario (natural history data[19] used for first cycle rather than placebo data)	£6,127	This scenario is plausible because there was a clear placebo effect seen in the clinical studies[15,16] which cannot be expected to happen in routine practice.
Scenario 2: Utility values mapped from SF–6D clinical study data	£9,087	This scenario is plausible because utilities from SF–6D scores collected during the clinical studies[15,16] can be expected to appropriately reflect the patient population's quality of life.
Scenario 3: Relative risk of fracture from alternative sources	£8,785: Stewart et al. (1992)[24] £6,969: Parsons et al. (2009)[21] £6,816: Kim et al. (2017)[23] £6,544: Asplund et al. (2006)[20] £5,963: Rafiq et al. (2014)[22]	This scenario is plausible because the publications were all included in the base case utility calculation.
Scenario 4: Utility decrement of 2 to < 4 and ≥ 4 voids applied as an absolute decrement rather than relative decrement	£6,487	This scenario is plausible as it is an alternative based on the same data sources used in the base case.

The results of the deterministic sensitivity analyses show that the model is robust, with all ICERs staying below £10,000. The results are most sensitive to changes in discount rates, transition probabilities for Noqdirna® and no treatment after 3 months, and probability of remission and recurrence.

Probabilistic sensitivity analysis suggests a mean ICER of £8,407 and a probability of Noqdirna® being cost-effective of 95% at a willingness-to-pay threshold of £20,000 and 98% at £30,000.

4.1.3 AWTTC critique

The results of the base case cost-utility analysis show that using Noqdirna® is more costly but produces increased quality of life compared with no treatment in people aged 65 years and older who have symptomatic nocturia due to nocturnal polyuria. This results in a base case ICER of £6,989 per QALY gained. The sensitivity analyses show that the results are robust with a probability of cost-effectiveness of 95% at the £20,000 willingness-to-pay threshold and 98% at the £30,000 threshold. Scenario analyses using alternative data sources for key parameters suggest ICERs of from £5,963 to £9,087 per QALY gained.

Strengths of the economic analysis:

- In the absence of other licensed treatments for the patient population over 65 years, no treatment appears to be an appropriate comparator for the cost-utility analysis for this patient group. The model is well constructed, logically laid out and appears robust. Methods used in the model and for data population are transparent, clearly described and well referenced.
- Extensive deterministic and probabilistic sensitivity analyses are conducted to investigate the effects of parameter uncertainty on the results.

Limitations of the economic analysis:

- The model uses data from the placebo arm of the clinical studies[15,16] in the first cycle (first 3 months) only and applies published data[19] thereafter. This approach was chosen because there was an evident placebo effect in the studies with 37% of men and 60% of women who had moderate nocturia and went into remission after receiving placebo for 3 months. The company says that this contradicts recent natural history data demonstrating that the resolution rate of nocturnal polyuria in older people is 9–12% after 2 years[19] and suggests that it might be an artefact of a well-monitored program motivating people to better adhere to the lifestyle advice. In practice, people would be given the advice as a one-off and adherence would be expected to be much lower. Consequently, the company states that this placebo effect would not be seen in practice[1].
- Data from a natural history study of nocturnal polyuria[19] were used to generate transition probabilities for the no treatment group after the first 3 months. The longitudinal study involved 1,688 Dutch men with nocturnal polyuria. It is unclear how generalisable the results of this study are to the Welsh population.
- Transition probabilities for women were derived by adjusting the transition rates for men taken from the natural history study[19] by the proportion of remissions between men and women observed in the clinical studies[15,16]. Although this appears to be an appropriate way to get the required data, the amount of data manipulation and assumption will introduce bias.
- Although data suggest that 25% of people experiencing a hip fracture in Wales die within the following year[38], the model only considers increased mortality in the cycle during which the fracture occurs. The company states that this is due to computational complexity and the chosen model structure. This limitation will underestimate the mortality in both arms and therefore underestimate QALY gain in the Noqdirna® arm because the probability of fracture is expected to be lower, resulting in a more conservative ICER.
- The probability of fractures in the nocturnal polyuria health states was calculated as the average of risk ratios reported in several relevant publications identified during a literature review conducted by the company. No indirect comparison or meta-analysis were done. This approach will therefore introduce bias because any study and population heterogeneity will be unaccounted for.
- The company suggests that in a small number of people with nocturnal polyuria, symptoms spontaneously resolve temporarily through a natural fluctuation of the condition rather than the effect of treatment. These patients are assumed to enter remission and withdraw from treatment. Although such patients can develop symptoms again at a later time, they are not re-started on treatment because the model does not allow tracking of individual patients. This may underestimate the effect of treatment and introduce bias because these patients might restart treatment if the condition worsens with age.
- The model assumes sustained efficacy of Noqdirna® over a patient's lifetime. To date, available data are restricted to 92 weeks. Therefore, there are no longer term data to support this assumption.
- The company's cost-minimisation analysis for comparing Noqdirna® with off-label desmopressin acetate preparations assumes equivalence of treatment effects and adverse events. The company states that hyponatraemia increases with higher doses of off-label desmopressin acetate preparations which is not considered in the calculations. The cost-minimisation analysis is therefore inappropriate and will underestimate the cost-effectiveness of Noqdirna®.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-utility of Noqdirna® for the treatment of adults aged 65 and over with symptomatic nocturia caused by nocturnal polyuria.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The prevalence of nocturia is estimated as 35.2% in men and 35.6% in women[39]. Most people with nocturia (81.3%) have idiopathic nocturnal polyuria[40] and 11.2% are thought to seek treatment[41]. Applying these values to the projected population of Wales aged 65 years and older in 2017[42] gives a current prevalence of 20,752. Annual incidence and mortality are modelled indirectly through population growth by applying the prevalence to the projected population estimates of Wales aged 65 years and over for the years 2017 to 2021[42]. This results in 346 newly diagnosed cases in year 2, 342 in year 3, 300 in year 4, and 319 in year 5. Although existing desmopressin acetate formulations are not recommended for people over 65, it is assumed that 0.5% of eligible people are currently treated off-label, equating to approximately 100 people in Wales. Based on typical market uptake rates for new technologies, the company estimates uptake of Noqdirna® as 0.6% in year 1, increasing to 11.8% in year 5. The analysis considers a discontinuation rate of 4.6% for newly diagnosed people in their first year of treatment because of moderate and severe hyponatraemia and an annual remission rate of 4.4% from year 3 onwards.

The list price for a pack of 30 Noqdirna® lyophilisate tablets is £15.16, which equates to an annual cost per patient of £184.45. The cost of off-label desmopressin acetate formulations for one year is calculated as £341.68 using published unit costs weighted according to market share[37]. Monitoring of serum sodium levels is needed before starting any desmopressin acetate treatment, during the first week of treatment and at one month after starting treatment, and is assumed to cost £33.31 per patient. A reduction in fall-related fractures due to improving nocturia symptoms with any desmopressin acetate formulation is incorporated in the calculations as an annual saving in healthcare costs per patient of £27.34 based on results from the cost-utility model.

5.1.2 Results

Table 5 shows the estimated net budget impact presented by the company. Introducing Noqdirna® is estimated to result in cost savings of £13,043 in year 1 but cost increases between £12,036 and £435,050 during years 2 to 5. The total budget impact over 5 years is expected to be in the region of £914,425.

Table 5. Company-reported costs associated with using Noqdirna®

	2017	2018	2019	2020	2021
Number of eligible patients (all licensed indications)	20,752	21,098	21,439	21,739	22,058
Uptake of new medicine (%)	0.6	1.2	4.3	9.3	11.8
Number of patients receiving new medicine allowing for discontinuations	119	247	851	1,883	2,463
Medication costs	£21,909	£45,623	£156,919	£347,270	£454,274
Savings from displaced medicines	£35,452	£36,043	£36,627	£37,139	£37,683
Net medicine acquisition costs	–£13,543	£9,579	£120,292	£310,132	£416,591
Net monitoring costs	£500	£2,456	£17,567	£32,392	£18,459
Net costs	–£13,043	£12,036	£137,859	£324,523	£435,050

The company reports primary and secondary care cost savings of £411 in year 1 to £64,320 in year 5.

Changing the uptake rate of Noqdirna® and the market share of off-label desmopressin acetate by 10% per year and varying the cost of off-label desmopressin acetate according to the cheapest and most expensive formulations results in a budget impact over five years ranging from £740,450 to £963,458.

5.1.3 AWTTC critique

- The data sources and calculations used for the budget impact model provided by the company are generally well described and appropriate sensitivity analyses are undertaken.
- Because of the lack of available data, annual incidence and mortality are calculated indirectly through prevalence figures and general population growth. The company argues that considering the natural fluctuations of nocturnal polyuria in terms of incidence and remission, it was deemed too complex to include these parameters in the budget impact calculation. However, the chosen approach will introduce bias.
- The number of people receiving off-label desmopressin acetate preparations is based on an assumption made by the company. Any differences in actual off-label use will affect the results of the budget impact analysis.
- Cost reduction due to decreased frequency of falls in people treated with Noqdirna® is based on the undiscounted outputs of the cost-utility model which could overestimate this cost.
- Primary, secondary and tertiary care costs are not specified as they are reported as total costs. The company state that primary and secondary costs are mainly attributable to hip fracture, but the data are aggregated and cannot be verified.
- Uptake rates are estimates based on the company's experience and data on file not available for review. Any changes to the uptake rate will affect the budget impact of Noqdirna®.

5.2 Comparative unit costs

Annual acquisition costs of Noqdirna® are described in Table 6. To date, no other treatment options are licensed in the UK for treating symptomatic nocturia due to nocturnal polyuria in adults aged 65 years and older.

Table 6. Examples of acquisition costs of specific treatments for people aged 65 and over with symptomatic nocturia due to nocturnal polyuria

Regimens	Example doses	Approximate annual costs
Noqdirna® 25 microgram oral sublingual tablets (30 pack)	25 micrograms daily (in women) an hour before bedtime	£184.45 (£15.16 per pack)
Noqdirna® 50 microgram oral sublingual tablets (30 pack)	50 micrograms daily (in men) an hour before bedtime	£184.45 (£15.16 per pack)
No other regimens are licensed for use in this patient population. Costs and doses from British National Formulary, accessed March 2017[27]. Despite the higher dose in men, the medicine is priced the same for men and women.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, Noqdirna® for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 6 March 2017
Date range of evidence search: No date limits were applied to database searches.

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