Low dose desmopressin lyophilisate (Noqdirna) for nocturia in adults

LAY SUMMARY

Producing too much urine at night is the main cause of nocturia (the need to wake up at night to urinate). Although it affects a large number of men and women, particularly as they get older, nocturia is often not recognised as a separate condition and treated with medications for overactive bladder or enlarged prostate (benign prostatic hyperplasia).

Current approaches to treating nocturia include advice on lifestyle modifications and various drugs, including desmopressin. However, currently available desmopressin tablets are not licensed for use in patients over 65 years, the main group who suffer from nocturia. If licensed, desmopressin lyophilisate will offer an additional effective oral treatment option for older adults with nocturia.

NIHR HSRIC ID: 7097
TARGET GROUP

- Nocturia: idiopathic nocturnal polyuria; symptomatic; in adults – as a sole agent or combination treatment.

TECHNOLOGY

DESCRIPTION

Desmopressin lyophilisate (Noqdirna [UK]; Nocturna [EU]; FE106483; Minirin Melt; DDAVP Melt) is a synthetic analogue of vasopressin formulated in an orally disintegrating sublingual tablet formulation that acts as an antidiuretic, thereby reducing urine output. In phase III clinical trials, desmopressin lyophilisate is administered orally at 25μg (women) at night approximately 1 hour before bedtime\(^1\).

Desmopressin acetate in various oral and nasal spray formulations is currently licensed in the EU for the treatment of vasopressin-sensitive cranial diabetes insipidus, post-hypophysectomy polyuria/polydipsia, nocturia associated with multiple sclerosis, and for primary nocturnal enuresis\(^2\). Desmopressin lyophilisate as DDAVP Melt (sublingual) is specifically licensed for the treatment of post-hypophysectomy polyuria/polydipsia, and central diabetes insipidus, while DesmoMelt (sublingual) is specifically licensed for primary nocturnal enuresis in children aged 5 years and older and adults up to 65 years of age who have normal urine concentrating ability\(^2\).

The recognised adverse effects (AEs) associated with desmopressin acetate include headache, stomach pain and nausea. Isolated cases of allergic skin reactions and more severe general allergic reactions have also been reported as well as very rare cases of emotional disorders, including aggression in children\(^2\). Treatment with desmopressin without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with accompanying symptoms of headache, nausea, vomiting, weight gain, decreased serum sodium and in severe cases, convulsions\(^2\). The recognised AEs associated with desmopressin lyophilisate are reportedly similar to those listed above\(^a\).

Desmopressin acetate and desmopressin lyophilisate are also used off-label for treating nocturia or nocturnal polyuria in men and women with lower urinary tract symptoms\(^3\).

INNOVATION and/or ADVANTAGES

If licensed, desmopressin lyophilisate will offer a lower dose sublingual treatment option for adults with nocturia, including those aged over 65 years, where adverse event risk minimisation is important, particularly in regard to hyponatraemia.

DEVELOPER

Ferring Pharmaceuticals Ltd.

\(a\) Company provided information.
AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Nocturia, or frequent night time urination, is a common but poorly reported and largely misunderstood urological disorder in adults\(^4\). Traditionally, nocturia was viewed by health professionals as part of lower urinary tract symptoms (LUTS) associated with conditions such as overactive bladder syndrome (OAB) and benign prostatic enlargement (LUTS/BPE)\(^5\).\(^6\). Nocturia is considered one of the most bothersome symptoms of LUTS/BPE\(^5\). Many patients with overactive bladder have nocturia but most patients with nocturia do not have overactive bladder\(^6\). However, nocturia is now increasingly being recognised as a separate disorder with a multi-factorial aetiology/pathogenesis\(^5\).\(^6\). The causes of nocturia can be classified into bladder storage problems, increased urine output (polyuria) and sleep disturbance problems\(^7\). It is also seen as a symptom of many different underlying medical conditions (such as obstructive sleep apnoea, congestive heart failure and peripheral oedema) and may also be caused or exacerbated by certain medications (such as diuretics, calcium channel blockers)\(^8\). The complex and overlapping causes of nocturia make it a very challenging condition to manage\(^9\).

Nocturia has a profound impact on a patient’s quality of life\(^10\). For some, nocturia may have little health impact, but for others it is bothersome, debilitating and associated with disturbed sleep, reduced well-being, and increased morbidity\(^9\). The consequence of sleep deprivation leads to daytime fatigue, poor concentration, memory impairment, mood alterations and affects work performance\(^8\). Chronically impaired sleep has been associated with increased mortality and a 25% increased risk of falls in older people\(^9\).

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to the following Department of Health policy area:

CLINICAL NEED and BURDEN OF DISEASE

Nocturia is an underreported condition and therefore the true extent of the problem is likely to be underestimated\(^4\). Over one-third of adults over the age of 30 wake up at least twice at night to urinate\(^11\). The prevalence of nocturia increases with age in both men and women. The most affected are older adults, with around 70% of those aged 70 years and older affected by nocturia in comparison to around 30% of adults aged 20-40 years\(^10\).

Nocturia is one of the most common causes of disrupted sleep, with 80% of people who complain of a disturbed night’s sleep reporting that nocturia is the main reason they wake up in the night\(^12\). Around 75% of patients with nocturia believe their condition is troublesome\(^13\).

In 2014-15, there were 4,697 hospital admissions for polyuria (ICD-10 R35) resulting in 1,374 bed days and 4,812 finished consultant episodes\(^14\).
The population likely to be eligible for treatment with desmopressin lyophilisate could not easily be estimated from routine publicly available sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

**Other Guidance**

**CURRENT TREATMENT OPTIONS**

Due to the multifactorial nature of nocturia, it is important to identify the specific aetiology and focus on the underlying pathophysiology. Current management of the symptoms of nocturia, or nocturia where no specific cause can be identified includes lifestyle modifications, treatment with alpha-blockers, antimuscarinic therapies, and antidiuretics:

- Lifestyle or behavioural modifications include: voiding before bedtime, limiting caffeine and alcohol intake, adjusting medication timing, use of protective undergarments, and use of sleep medications/aides.
- Loop diuretics, e.g. furosemide, bumetanide, and torsemide. Afternoon dosing may promote excess diuresis during the day, rather than at night. Side effects may include dehydration, gout, low serum sodium or low potassium concentrations, dizziness and hypotension.
- Antimuscarinic therapy may reduce nocturia by increasing bladder capacity, e.g. darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride. These should be considered for patients with overactive bladder.
- Antidiuretic therapy such as desmopressin, taken last thing before sleep, may be recommended off-label for nocturnal polyuria. Whilst recommended for the treatment of
nocturia, use of the currently available formulations of desmopressin acetate and desmopressin lyophilisate are on an off licence basis for older adults\(^b\). Current guidance suggests using an existing sublingual formulation of desmopressin at a starting dose of 25µg in women and 50µg in men, irrespective of age. A higher dose should only be used with caution. All patients should be monitored for hyponatremia\(^{22,23}\). Current NICE guidelines suggest offering oral desmopressin formulations to men with nocturnal polyuria only if other medical causes have been exhausted\(^{24}\).

A clinical expert stated that one of the main problems faced by clinicians is that the current licence restricts use to patients under the age of 65 where the risk of hyponatraemia is less pronounced\(^c\). However, the majority of patients that present with bothersome nocturia to urological practice are above that age. In such patients, desmopressin acetate (such as sublingual DDAVP preparations) may be used, however this is done in a cautious manner with monitoring of serum sodium levels at baseline day 3, day 7, week 3, month 3, month 6 and every 6 months thereafter, as well as at every dose change to ensure they do not develop late hyponatraemia\(^d\). Expert opinion notes that there is evidence that hyponatraemia is more harmful in patients over the age of 80, and in such cases desmopressin would not normally be recommended\(^d\). However, other experts believe that desmopressin is currently the only medication available for nocturia for which there is good evidence that it helps to improve quality of life for patients\(^d\).

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01223937, COMFORT, FE992026 CS40; females; desmopressin vs placebo; phase III.</th>
<th>NCT01262456, FE992026 CS41; males; desmopressin vs placebo; phase III.</th>
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<td>Sponsor</td>
<td>Ferring Pharmaceuticals.</td>
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<td>Status</td>
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<tr>
<td>Source of information</td>
<td>Publications(^{25}), trial registry(^{1}).</td>
<td>Publication(^{26,27}), trial registry(^{28}).</td>
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<td>Location</td>
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<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<td>Participants</td>
<td>n=268; ≥18 yrs; females; at least 2 voids every night in a consecutive 3-day period during screening; no evidence of severe daytime voiding dysfunction defined as: urge urinary incontinence (more than 1 episode/day in the 3-day diary period), urgency (&gt;1 episode/day in the 3-day diary period), and frequency (&gt; 8 daytime voids/day in the 3-day diary period); no interstitial cystitis; no urinary retention or a post void residual volume &gt;150 mL as confirmed by bladder ultrasound performed after suspicion of urinary retention; no habitual or psychogenic polydipsia (fluid intake resulting in a urine production ≥40 mL/kg/24 hrs); no central or nephrogenic diabetes insipidus; no syndrome of inappropriate anti-diuretic hormone secretion; no history of urologic malignancies or significant genitourinary</td>
<td>n=395; ≥18 yrs; males; at least 2 voids every night in a consecutive 3-day period during screening; no evidence of severe daytime voiding dysfunction defined as: urge urinary incontinence (&gt; 1 episode/day in the 3-day diary period), urgency (&gt;1 episode/day in the 3-day diary period), and frequency (&gt;8 daytime voids/day in the 3-day diary period); no interstitial cystitis; no chronic prostatitis/chronic pelvic pain syndrome; no suspicion of bladder outlet obstruction (BOO) or a urine flow less than 5 mL/s by uroflowmetry performed after suspicion of BOO; no surgical treatment, including transurethral resection, for BOO or benign prostatic hyperplasia within the past 6 mths; no urinary retention or a post void residual volume in excess of 250mL as confirmed by bladder ultrasound</td>
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\(^{b}\) Company provided information.
\(^{c}\) Expert personal opinion.
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<th>Horizon Scanning Research &amp; Intelligence Centre</th>
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<td><strong>tract pathology; no uncontrolled diabetes mellitus; no previous desmopressin treatment for nocturia; serum creatinine must be within normal limits and estimated glomerular filtration rate ≥50 mL/min; no history of obstructive sleep apnoea; no hepatic and/or biliary disease.</strong></td>
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<td><strong>Follow-up</strong></td>
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An increasing incidence of hyponatremia with increasing dose was found, and at the highest dose level (100μg), decreases in serum sodium were approximately twofold greater in women over 50 yrs than in men. No other new AE signals were observed. The frequency and type of AEs observed were similar in the parent and extension studies.

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**ESTIMATED COST and IMPACT**

**COST**

Desmopressin acetate is already marketed in the UK; a pack of 90x100μg oral tablets costs £44 and a pack of 100x60μg sublingual disintegrating tables (as DDAVP Melt) costs £51.33.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- □ Reduced mortality/increased length of survival
- □ No impact identified
- ❏ Reduced symptoms or disability
- ❏ No impact identified
- ❏ Other: expert opinion judges overall desmopressin is a safe drug with the main side effect being dilutional hyponatremia which can result in seizures. However with careful monitoring this can be kept to a minimum and the drug stopped if the serum sodium levels fall.

**Impact on Health and Social Care Services**

- □ Increased use of existing services
- □ Decreased use of existing services
- □ Re-organisation of existing services
- □ Need for new services
- □ No impact identified
- □ None identified

**Impact on Costs and Other Resource Use**

- ❏ Increased drug treatment costs
- □ Other increase in costs
- □ Other reduction in costs
- ❏ Reduced drug treatment costs: low dose desmopressin lyophilisate may also reduce treatment costs where OAB or BPH treatments are used in patients with undiagnosed nocturnal polyuria.
- □ None identified

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*d Expert personal opinion.
*e Company provided information.
Other Issues

☑ Clinical uncertainty or other research question identified: expert stated there is a real need for desmopressin treatment in patients with nocturia. However, it should not be used without the appropriate baseline urological assessment in patients with nocturia.

☐ None identified

REFERENCES

20 EAU patient information. Nocturia.

Footnote: †Expert personal opinion.