Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING
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Fedovapagon for nocturia in men with benign prostatic hyperplasia

NIHRIO ID	6800	**NICE ID**	9849
Developer/Company	Vantia Therapeutics	**UKPS ID**	N/A

Licensing and market availability plans	The regulatory filing and marketing/launch plans of fedovapagon for nocturia in men with benign prostatic hyperplasia could not be established as at the time of producing this briefing

SUMMARY

Fedovapagon is in clinical development as an oral treatment for nocturia in men with benign prostate enlargement. Nocturia is a common symptom in men who have enlarged prostates. Nocturia is generally defined as excessive or disruptive (either due to the volume of urine or frequency of trips to the toilet) night-time urination which disrupts sleep and impairs quality of life. There are currently no specific treatments for nocturia in men with enlarged prostates. Instead, nocturia is currently managed with drugs prescribed to treat the general symptoms of enlarged prostates, which are rarely effective in treating nocturia and can have side effects. As this is a common symptom in men with this condition, there is a clinical need for this type of treatment.

Fedovapagon works directly in the collecting ducts of the kidney by binding to, and activating receptors that causes the kidneys to reabsorb water from urine as it passes towards the bladder. If fedovapagon is administered before going to bed the result is less urine produced overnight. Therefore, if licensed, fedovapagon would be the first medicinal product specifically for the treatment of nocturia in men with enlarged prostates.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to comment.

PROPOSED INDICATION

Nocturia in men with benign prostatic hyperplasia (BPH)[1]

TECHNOLOGY

DESCRIPTION

Fedovapagon (VA106483) is a novel small molecule antidiuretic that acts directly in the collecting ducts of the kidney by binding to, and activating, vasopressin V2 receptors. Activation of the V2 receptors causes the kidneys to reabsorb water from urine as it passes towards the bladder. If fedovapagon is dosed before going to bed the result is less urine produced overnight. Men with nocturia commonly produce large volumes of urine at night and it is hypothesized that this leads to multiple trips to the bathroom to empty their bladder. It is hoped that producing less urine overnight will reduce the number of trips to the bathroom and, in turn, increase sleep time.[2]

Fedovapagon is currently being developed for the treatment of nocturia, a common condition in those with benign prostatic hyperplasia (BPH). In the phase III trial (EQUINOC, NCT02637960) 2mg fedovapagon is given orally, once daily for 12 weeks.[1]

INNOVATION AND/OR ADVANTAGES

Current nocturia treatment options are limited for men with BPH. Whilst most patients are advised to limit evening fluid intake this approach is of limited value and whilst pharmacological treatments, such as alpha blockers are administered, they have limited, if any, efficacy and no regulatory approval for the treatment of nocturia. The peptide drug, desmopressin, is used for the treatment of nocturia in some parts of the world but has shown a risk for hyponatremia, especially in elderly patients. As a result there is a significant population of patients seeking alternative treatments.[2]

If licensed, fedovapagon would provide a novel treatment option specifically for nocturia in men with BPH.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Fedovapagon does not currently have Marketing Authorisation in the EU/UK for any indication.[3]

PATIENT GROUP

DISEASE BACKGROUND

Nocturia, or frequent night-time urination, is a common urological disorder in adults. The definition of what constitutes nocturia vary widely, but generally definitions refer to night-time urination which entails some degree of impairment and urinary frequency considered excessive or disruptive (either due to the volume of urine voided or number of trips to the toilet). As there is no agreed definition of normal urination, nocturia is often overlooked by patients and healthcare professionals until the symptom becomes unbearable or affects quality of life.[4]

Nocturia is a common symptom of benign prostatic hyperplasia (BPH), a condition in men in which the prostate becomes enlarged. The main risk factors for development of BPH include increasing age and hormonal level balance.[5, 6]

Sleep disruption as a result of nocturia can affect many aspects of a patient's quality of life including contributing to fatigue, memory deficits, mood changes, impaired work related productivity, increased risk of heart disease, gastrointestinal disorders and sometimes potential injury by falls.[4, 6]

CLINICAL NEED AND BURDEN OF DISEASE

BPH rarely occurs before 40 years of age and is estimated to affect approximately 50% men between 51 and 60 years old and up to 90% of men older than 80 years old.[7] There are approximately 3.2 million men in the UK who experience symptoms of BPH.[8]

In a study of 505 newly diagnosed patients with symptomatic BPH, 359 (71%) reported that they arose at least twice for urination at night.[9]

According to the Hospital Episode Statistics for 2016-17, there were 32,540 admissions, 34,567 finished consultant episodes (FCE) and 51,042 FCE bed days due to hyperplasia of prostate (ICD10: N40).[10]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Treatment for BPH depends on how severe the symptoms are. Treatment usually starts with lifestyle changes which include drinking fewer fizzy drinks, alcohol, caffeine and artificial sweeteners, reducing fluid intake before bed, double voiding, reviewing medication (as some medications can make urinary symptoms worse), consuming more fruit and fibre, using absorbent pads or sheaths and bladder training (exercise programmes that aims to help patients go longer without going to the toilet). If lifestyle changes do not work or are not suitable, medications can be offered.[11] Surgery can be a treatment option if no other treatment options have worked.[12]

CURRENT TREATMENT OPTIONS

- *First line:*[12]
  - 5-alpha reductase inhibitors (e.g. dutasteride or finasteride) – NICE recommend this for the treatment of men with lower urinary tract symptoms (LUTS) in men with prostates larger than 30g or a PSA level greater than 1.4ng/ml who are at high risk of progression
  - Alpha Blockers (alfuzosin, doxazosin, tamsulosin or terazosin) – NICE recommend this for men with moderate to severe LUTS
  - 5-alpha reductase inhibitors in combination with alpha blockers – NICE recommend this for men with bothersome moderate to severe LUTS and prostates larger than 30g or a PSA level greater than 1.4ng/ml.
- *Second line:*[12, 13]
  - Anticholinergic drugs (e.g. oxybutynin immediate release, tolterodine immediate release or darifenacin once daily preparation) – recommended for symptoms which persist after alpha-blocker monotherapy

- Oral desmopressin – recommended if symptoms remain bothersome after lifestyle changes and loop diuretics

PLACE OF TECHNOLOGY

If licensed, fedovapagon would be the first treatment specifically for the treatment of nocturia in men with BPH, a common symptom of BPH.[2]

CLINICAL TRIAL INFORMATION

Trial	EQUINOC, NCT00108883, 483-013; fedovapagon vs placebo; phase II/III.
Sponsor	Vantia Ltd
Status	Completed and Published in abstract
Source of Information	Trial registry[1], abstract[14]
Location	USA
Design	Randomised, placebo-controlled, triple masked, parallel assignment
Participants	n=432; aged 18 years and older; males; benign prostatic hyperplasia; persistent nocturia; despite lifestyle modification advice including appropriate fluid management.
Schedule	Participants were randomised to one of two treatment arms: 1. Fedovapagon 2mg given orally, once daily for 12 weeks 2. Fedovapagon placebo given orally, once daily for 12 weeks
Follow-up	Active treatment for 12 weeks
Primary Outcomes	• Change in the mean number of night-time voids [Time Frame: 12 weeks] • Change in mean patient reported nocturia bother score [Time Frame: 12 weeks]
Secondary Outcomes	• Change in the mean number of night-time voids [Time Frame: 1 week and 4 weeks] • Change in mean patient reported nocturia bother score [Time Frame: 1 and 4 weeks] • Change in mean night-time urine production, absolute and as a proportion of 24 hour urine production [Time Frame: 2 months] • Change in mean functional bladder capacity [Time Frame: 2 months] • Change in International Prostate Symptom Score (IPSS) [Time Frame: 4 and 12 weeks] • Change in N-QOL Score [Time Frame: 4 and 12 weeks] • Number and type of Adverse Events [Time Frame: 12 weeks]
Key Results	The trial met its first co-primary endpoint demonstrating a reduction in nocturnal voids from baseline (waking and urinating) after 12 weeks of treatment (p=0.004) and showed a statistically significant effect when all time points (weeks 1, 4 and 12) were pooled (p<0.001). The second co-primary endpoint, change in the patient reported outcome score, did not show a statistically significant effect at week 12 (p=0.118) although, when all time points were considered, the pooled result suggested a significant effect of treatment over the entire treatment period (p=0.034). The clinical significance of treatment was supported by statistically significant results for other endpoints at week 12, including time to first void (p<0.001), nights when patients have 0 or 1 voids (p=0.038) and patients who reduce their voids by 50% (p=0.007).[14]

Adverse effects (AEs)	It was reported that Fedovapagon was generally well tolerated.[14]
Expected reporting date	-

ESTIMATED COST

The cost of fedovapagon is not yet known.

ADDITIONAL INFORMATION

Vantia Therapeutics did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Lower urinary tract symptoms in men: management (CG97). May 2010. Last updated June 2015.
- NICE quality standards. Lower urinary tract symptoms in men (QS45). September 2013.
- NICE interventional proceedures guidance in development. Transurethral water jet ablation for lower urinary tract symptoms caused by benign prostatic hyperplasia [GID-IPG10078]. Expected publication date TBC.
- NICE interventional proceedures guidance. Prostatic urethral temporary implant insertion for lower urinary tract symptoms caused by benign prostatic hyperplasia. Expected publication date TBC.
- NICE interventional proceedures guidance. Transurethral water vapour ablation for lower urinary tract symptoms caused by benign prostatic hyperplasia (IPG625). August 2018.
- NICE interventional proceedures guidance. Prostate artery embolisation for lower urinary tract symptoms caused by benign prostatic hyperplasia (IPG611). April 2018.
- NICE interventional proceedures guidance. Insertion of prostatic urethral lift implants to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia (IPG475). January 2014.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy: Sacral Nerve Stimulation for Overactive Bladder. NHS England E10/P/b. July 2015.

OTHER GUIDANCE

- NICE Clinical Knowledge Summaries. LUTS in men. February 2015.[12]
- Royal College of Surgeons. Commissioning guide: Lower urinary tract symptoms. 2013[15]

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[11] NHS Choices. *Treatment – Benign prostate enlargement.* Available from: https://www.nhs.uk/conditions/prostate-enlargement/treatment/ [Accessed 29 August 2018]

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[14] Vantia Therapeutics. *Vantia Therapeutics announces Positive Results from its Phase III EQUINOC® Study, a Pivotal Trial with Fedovapagon for the Treatment of Nocturia in Men with Benign Prostatic Hyperplasia. 3 October 2017*. Available from: https://www.vantia.com/assets/doc/vantia_pr_031017.pdf [Accessed 23 August 2018].

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