Health Technology Briefing
February 2023

Vibegron for treating overactive bladder

Company/Developer	Pierre Fabre Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 35904	NICE ID: 11849	UKPS ID: 667201

Licensing and Market Availability Plans

Currently in clinical development.

Summary

Vibegron is in clinical development for the treatment of Overactive Bladder (OAB). OAB can occur with a range of symptoms, including a sense of urgency to urinate, this can be accompanied with urinary incontinence, called wet OAB or no urinary incontinence, called dry OAB. Most often patients with OAB also experience increased frequency of urination and nocturia (waking through the night to urinate). Healthcare providers in England try to alleviate symptoms of OAB by advising patients to undertake bladder training exercises and to alter other lifestyle habits. If this does not improve symptoms, patients may be prescribed a medicinal product called anticholinergics, but the long-term side effects of taking these are not fully understood and carry a high risk of adverse events.

Vibegron tries to alleviate symptoms of OAB by binding to specific receptors on muscle cells that are found in the bladder. Once the molecule binds to the cell receptor, it prevents the muscles from prematurely contracting which creates a sense of urgency to urinate often. Ensuring the muscles stay relaxed means the bladder can fill completely before urination. If licenced, the medicinal tablet vibegron may provide an additional treatment option for patients with OAB.

Proposed Indication

Treatment of adult patients with symptoms of overactive bladder (OAB).[1]

Technology

Description

Vibegron (USA brand name GEMTESA®), a new molecular entity/analgesic is a beta-3 adrenergic agonist that selectively binds to and activates beta-3 adrenergic receptors which are expressed on cells of detrusor smooth muscle located in the bladder. Binding causes the detrusor smooth muscle to relax during the storage phase of micturition, increasing bladder storage capacity and preventing involuntary contraction.[2-4]

Vibegron is in clinical development for the treatment of OAB. Vibegron was administered orally (75mg/day) over a 12-week treatment period during the pivotal phase III clinical trial (EMPOWUR).[1]

Key Innovation

In England, anticholinergic drugs (sometimes called anti-muscarinics)[5] are generally recommended as a treatment option following conservative interventions to manage symptoms of OAB.[6,7] However, a large body of literature suggests the tolerability profile is poor, and possible long-term adverse outcomes, such as dementia and Alzheimer's are subject to uncertainty. Adverse effects are of particular concern in elderly patients and people taking multiple anticholinergic medications. Documented adverse effects include; dry mouth, constipation, dizziness, impaired cognitive function, increased risk of mortality and falls.[3,5,6,8] Because of the high risk of adverse events, healthcare providers are increasingly advised to avoid prescribing anticholinergic drugs or to assess the patients total anticholinergic load (polypharmacy) before prescribing.[5]

Vibegron has being generally well tolerated with an adverse event profile comparable to the placebo controlled arm.[3] If licensed, vibegron may offer an additional treatment option for adult patients with OAB in whom antimuscarinic drugs are contraindicated or clinically ineffective or have unacceptable side effects.

Regulatory & Development Status

Vibegron does not currently have marketing authorisation in the EU/UK for any indication.

Vibegron is in phase II/III clinical development for neurogenic detrusor overactivity and OAB in men with benign prostatic hyperplasia.[9]

Patient Group

Disease Area and Clinical Need

OAB is characterised by an urgency to urinate, which can be followed by an episode of incontinence (wet OAB) or without incontinence (dry OAB). In addition, increased urinary frequency and nocturia are common symptoms.[10,11] The causes of overactive bladder are not fully understood, but some factors which may increase a person's risk are: high alcohol or caffeine intake, low fluid intake, constipation, neurological conditions, certain medications, BMI over 30, ageing and familial history.[12,6]

Epidemiological findings between 1987 and 2004 suggest the overall prevalence of OAB-related symptoms in the United Kingdom (UK) was 3.87 per 1000 persons, with an incidence of 2.79 per 1000 person-years.[13] In England, 2021-22, there were 25,773 finished consultant episodes (FCE) and 24,667 admissions for other specified disorders of the bladder, including overactivity (ICD-10 code N32.8) resulting in 15,043 FCE bed days and 18,734 day cases.[14]

Recommended Treatment Options

Conservative interventions, such as bladder training, are recommended as first-line treatment for symptoms of overactive bladder. If symptoms persist, a prescription of medicinal anticholinergics (oxybutynin, tolterodine and darifenacin) is recommended. In patients who experience no improvement or poor tolerability to anticholinergics an alternative medicinal product, Mirabegron, may be prescribed. Mirabegron is the only beta 3-adenoceptor agonist with marketing authorisation in the UK to treat symptoms of overactive bladder in adults.[15]

Clinical Trial Information

Trial	**EMPOWUR; NCT03492281;** An International Phase 3, Randomised, Double-Blind, Placebo- and Active (Tolterodine)-Controlled Multicenter Study to Evaluate the Safety and Efficacy of Vibegron in Patients With Symptoms of Overactive Bladder **Phase III** - Completed **Location(s):** Four EU countries, USA and Canada **Study completion date:** February 2019	**EMPOWUR Extension: NCT03583372;** An International Phase 3, Randomised, Double-Blind, Active (Tolterodine)-Controlled Multicenter Extension Study to Evaluate the Long-Term Safety and Efficacy of Vibegron in Patients With Symptoms of Overactive Bladder **Phase III** - Completed **Location(s):** USA **Study completion date:** July 2019
Trial Design	Phase III, randomised, double-blind, placebo and active controlled multicentre study.	Phase III, randomised, blind, placebo and active controlled multi-centre extension study.
Population	N=1530 (actual); Male and females over the age of 18 who have symptoms of OAB for at least 3 months prior to the screening visit.[3]	N=506 (actual); Male and Female adults who participated in and demonstrated 80% compliance in study RVT-901-3003 (NCT03492281).
Intervention(s)	Single orally administered 75mg tablet of vibegron per day for 12 weeks plus placebo (active comparator)	Single orally administered 75mg tablet of vibegron per day plus placebo (active comparator)

Comparator(s)	• Two matched placebos • Tolterodine tartrate ER (one oral dose of tolterodine tartrate ER for 4mg for 12 weeks) plus matched placebo	• Tolterodine plus matched placebo • Extended release tolterodine tartrate
Outcome(s)	The primary outcome measures are: • Change from baseline at week 12 in the average number of micturitions per 24 hours in all OAB participants • Change from baseline at week 12 in the average number of urge urinary incontinence (UUI) episodes per 24 Hours in OAB wet participants See trial record for full list of other outcomes	Number of participants with the indicated type of treatment-emergent adverse events (up to 56 weeks). See trial record for full list of other outcomes
Results (efficacy)	See trial record	See trial record
Results (safety)	See trial record	See trial record

Estimated Cost

The cost of vibegron was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Lower urinary tract symptoms in men: management (CG97). June 2015.
- NICE guideline. Urinary incontinence and pelvic organ prolapse in women: management (NG123). June 2019.
- NICE technology appraisal. Mirabegron for treating symptoms of overactive bladder (TA290). June 2013.

NHS England (Policy/Commissioning) Guidance

- NHS Oxfordshire Clinical Commissioning Group. The management of overactive bladder syndrome. [16]

Other Guidance

- American Urological Association Education and Research. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019.[17]
- Canadian Urological Association. CUA Guideline on adult overactive bladder. 2017.[18]

Additional Information

References

1 Clinicaltrials.gov. *A Study to Examine the Safety and Efficacy of a New Drug in Patients With Symptoms of Overactive Bladder (OAB) (Empowur)*. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03492281 [Accessed 17 January 2023].

2 U.S. Food and Drug Adminsitration (FDA). *Drug Trial Snapshot: GEMTESA Prescribing Information*. 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213006s000lbl.pdf [Accessed 17 January 2023].

3 Staskin D, Frankel J, Varano S, Shortino D, Jankowich R, Mudd PN, Jr. International Phase III, Randomized, Double-Blind, Placebo and Active Controlled Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder: EMPOWUR. *J Urol*. 2020;204(2):316-24. Available from: https://doi.org/10.1097/JU.0000000000000807.

4 Igawa Y, Aizawa N, Michel MC. β(3) -Adrenoceptors in the normal and diseased urinary bladder-What are the open questions? *Br J Pharmacol*. 2019;176(14):2525-38. Available from: https://doi.org/https://doi.org/10.1111%2Fbph.14658.

5 PrescQIPP Community Interst Company. *Anticholinergic drugs*. 2016. Available from: http://www.derbyshiremedicinesmanagement.nhs.uk/assets/Clinical_Guidelines/Formulary_by_BNF_chapter_prescribing_guidelines/BNF_chapter_4/Anticholinergics_drugs.pdf [Accessed 18 January 2023].

6 National Institute for Health and Care Excellence (NICE). *Urinary incontinence and pelvic organ prolapse in women: management: NICE Guideline [NG123]*. 2019. Available from: https://www.nice.org.uk/guidance/ng123/resources/urinary-incontinence-and-pelvic-organ-prolapse-in-women-management-pdf-66141657205189 [Accessed 18 January 2023].

7 National Health Service (NHS). *Non-surgical treatment Urinary incontinence* 2019. Available from: https://www.nhs.uk/conditions/urinary-incontinence/treatment/ [Accessed 21 February 2023].

8 Fox C, Richardson K, Maidment ID, Savva GM, Matthews FE, Smithard D, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *J Am Geriatr Soc*. 2011;59(8):1477-83. https://pubmed.ncbi.nlm.nih.gov/21707557/.

9 ClinicalTrials.gov. *Vibegron | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 1, 2, 3*. 2022. Available from: https://clinicaltrials.gov/ct2/results?term=Vibegron&Search=Apply&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=0&phase=1&phase=2 [Accessed 17 January 2023].

10 Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology*. 2003;61(1):37-49. Available from: https://doi.org/10.1016/s0090-4295(02)02243-4.

11 Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn*. 2010;29(1):4-20. https://pubmed.ncbi.nlm.nih.gov/19937315/.

12 NHS Inform. *Urinary Incontinence*. 2021. Available from: https://www.nhsinform.scot/illnesses-and-conditions/kidneys-bladder-and-

prostate/urinary-incontinence/#symptoms-of-urinary-incontinence [Accessed 20 January 2023].

13 Odeyemi IA, Dakin HA, O'Donnell RA, Warner J, Jacobs A, Dasgupta P. Epidemiology, prescribing patterns and resource use associated with overactive bladder in UK primary care. *Int J Clin Pract*. 2006;60(8):949-58. https://pubmed.ncbi.nlm.nih.gov/16893437/.

14 NHS Digital. *Hospital Admitted Patient Care Activity*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity [Accessed 20 January 2023].

15 National Institute for Health and Care Excellence (NICE). *Mirabegron for treating symptoms of overactive bladder: Technology appraisal guidance [TA290]*. 2013. Available from: https://www.nice.org.uk/guidance/ta290?UNLID=407278557202312023025 [Accessed 20 January 2023].

16 Oxfordshire Clinical Commissioning Group. *The Management of Over Active Bladder Syndrome*. 2021. Available from: http://www.oxfordshireformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=7&SubSectionRef=07.04.02&SubSectionID=A100 [Accessed 21 January 2023].

17 Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. *Journal of Urology*. 2019;202(3):558-63. https://pubmed.ncbi.nlm.nih.gov/31039103/.

18 Corcos J, Przydacz M, Campeau L, Gray G, Hickling D, Honeine C, et al. CUA guideline on adult overactive bladder. *Canadian Urological Association journal = Journal de l'Association des urologues du Canada*. 2017;11(5):E142-E73. Available from: https://doi.org/10.5489/cuaj.4586.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.