NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Mirabegron for neurogenic detrusor overactivity in people aged 3 to 17 years

Company/Developer	Astellas Pharma

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 12969	NICE ID: 10730	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

Summary

Mirabegron is currently in clinical development for treatment of neurogenic detrusor overactivity (NDO) in children and adolescents aged 3 to 17 years old on clean intermittent catheterisation (CIC). NDO is a bladder dysfunction and can cause urinary symptoms such as frequency, urgency and urinary incontinence. Other symptoms of NDO include: pelvic pain, painful urination, incontinence, increased spasticity, autonomic dysreflexia, malaise, fever/chills, nausea, headache. Current treatment options for NDO in children and adolescent populations are very limited and are not well-tolerated.

Mirabegron is a beta-3-adrenergic-receptor agonist. It works by attaching to and activating beta-3 receptors that are found in the muscle cells of the bladder. In the phase III trial, mirabegron was administered orally. Mirabegron is an alternative treatment option to antimuscarinics (which block the activity of muscarinic receptors that play an important role in mediating the functions of the parasympathetic nervous system), with proven efficacy and safety in adults with NDO. Emerging evidence shows that mirabegron is a promising treatment in children populations as well. If licensed, mirabegron will offer an additional treatment option for children and adolescent patients with NDO who currently have few well-tolerated therapies available.

Proposed Indication

Treatment of NDO in children and adolescents aged 3 to 17 years old, who are on CIC.[1]

Technology

Description

Mirabegron (Betmiga) is a beta-3-adrenergic-receptor agonist. It works by attaching to and activating beta-3 receptors that are found in the muscle cells of the bladder.[2] Animal studies have shown that beta-3 receptor agonists exhibit a dose-dependent detrusor relaxation (mediated via up-regulation of cyclic-adenosine) during the storage phase of micturition. In this way, mirabegron can aid in the symptomatic relief of overactive bladder (OAB).[3]

Mirabegron is currently in clinical development for treatment of NDO in children and adolescents aged 3 to 17 years old, who are on CIC. In the phase III clinical trial (Crocodile; NCT02751931), mirabegron oral tablets were administered orally at initial dose of 25mg on day 1. At weeks 2, 4 or 8, participants were up-titrated to the paediatric equivalent dose of 50 mg in adults, orally once daily based on the given dose titration criteria. Following week 24, participants stayed on their individual dose level until week 52 end-of-study or end-of-treatment.[1] Those with body weight ≤35kg or who could not or did not want to take tablets received mirabegron as an oral suspension.[4]

Key Innovation

Currently there are few antimuscarinics that are approved for the treatment of NDO. Antimuscarinic drugs are associated with a number of anticholinergic adverse events (AEs), such as dry mouth, constipation, and urinary retention, which may limit adherence. Of particular concern in paediatric patients is the potential for impairment of cognitive development and learning, especially as anticholinergic central nervous system AEs are reportedly more common in paediatric patients compared with adults. Furthermore, adherence and persistence with antimuscarinic drugs are known to be suboptimal. While adherence may be of a lesser concern in younger patients, the fact that the vast majority of patients in this study (NCT02751931) found the tablets and oral solution to be good in terms of taste, smell and swallow acceptability is reassuring.[4]

Mirabegron, a β3-adrenoreceptor agonist, is an alternative treatment option to antimuscarinics, with proven efficacy and safety in adults with OAB. As mirabegron has a distinct mechanism of action, and is generally devoid of antimuscarinic AEs, it generally has a favourable safety profile. Mirabegron has also shown positive effects on urodynamic parameters in adult patients with NDO.[4] Furthermore, emerging evidence shows that mirabegron is a promising treatment in paediatric populations.[4-6] Therefore, if licensed, mirabegron will offer an additional treatment option for children and adolescent patients with NDO who currently have few well-tolerated therapies available.

Regulatory & Development Status

Mirabegron prolonged-release oral tablets has a Marketing Authorisation in the UK for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.[7]

Mirabegron does not currently have a Marketing Authorisation in the EU/UK for any indication in children and adolescents.

Mirabegron is in phase II/III clinical development for:[8]

- Overactive bladder
- Intracerebral hemorrhage
- Heart failure
- PreDiabetes
- Stent related symptoms

Patient Group

Disease Area and Clinical Need

NDO is a urodynamically measured bladder dysfunction caused by a lesion in the brain or spinal cord associated with a congenital condition (e.g., myelomeningocele), an acquired, stable condition (e.g., stroke, spinal cord injury), or an acquired, progressive condition (e.g., multiple sclerosis, Parkinson's disease, dementia). NDO is a neurogenic lower urinary tract dysfunction and can cause urinary symptoms such as frequency, urgency and urinary incontinence.[9] Other symptoms of NDO include: pelvic pain, dysuria, incontinence, increased spasticity, Autonomic Dysreflexia (AD), malaise, fever/chills, nausea, headache.[10]

Neurogenic bladder affects over 90% of patients with spinal cord injury, 50–80% of patients with multiple sclerosis and over 95% of patients with spina bifida.[11] Epidemiological data regarding NDO is strongly limited.[12] In England 2020-21, there were 1,919 finished consultant episodes (FCEs), of which 673 were for people aged 1-17 years, for neuromuscular dysfunction of bladder, unspecified (ICD-10 code: N31.9).[13]

Recommended Treatment Options

Oral oxybutynin and solifenacin succinate are the only licensed medicinal products for children over 5 years old with overactive bladder. Trospium standard release is licensed in children over 12 years old. There are also other treatments recommended for treatment of OAB in children over 5 years old, such as tolterodine and oxybutynin patch however, they are not licensed for use in children.[14,15]

Clinical Trial Information

Trial	**Crocodile;** NCT02751931, EudraCT2015-002876-25; An Open-label, Baseline-controlled, Multicenter, Phase 3 Dose-titration Study Followed by a Fixed-dose Observation Period to Evaluate Efficacy, Safety and Pharmacokinetics of Mirabegron in Children and Adolescents From 3 to Less Than 18 Years of Age With Neurogenic Detrusor Overactivity (NDO) on Clean Intermittent Catheterization (CIC) **Phase III –** Completed **Location(s):** 8 EU countries and other countries **Study Completion Date:** May 2019
Trial Design	Non-randomised, single group assignment, open label, baseline controlled
Population	N=91 (actual); patients 3 to 17 years old who suffer from NDO confirmed by urodynamic investigation at baseline; been using CIC for at least 4 weeks
Intervention(s)	• Prolonged-release oral tablets or granules for oral suspension mirabegron (children 3 to < 12 years)

	• Prolonged-release oral tablets or granules for oral suspension mirabegron (adolescents 12 to < 18 years)
Comparator(s)	No comparator
Outcome(s)	**Primary outcome measure:** Change from baseline in maximum cystometric capacity (MCC) at week 24 [Time frame: baseline and week 24] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

Mirabegron prolonged-release oral tablets are already licensed for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. NHS indicative price for 30 tablets of mirabegron of 25mg and 50mg is £29.00.[16]

Relevant Guidance

NICE Guidance

- NICE Technology appraisal guidance awaiting development. Oxybutynin hydrochloride for managing neurogenic detrusor overactivity in people 6 years and over with spinal cord injury or spina bifida [ID5089] (GID-TA10998). Expected date of issue to be confirmed.
- NICE technology appraisal. Mirabegron for treating symptoms of overactive bladder (TA290). June 2013.
- NICE clinical guideline. Urinary incontinence in neurological disease: assessment and management (CG148). August 2012.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- European Association of Urology. EAU Guidelines on Neuro-Urology. 2019.[17]
- European Association of Urology. EAU Guidelines on Neurogenic Lower Urinary Tract Dysfunction. 2009.[18]

Additional Information

Astellas Pharma Ltd. 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.

References

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