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Newcastle University

Health Technology Briefing
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Oxybutynin hydrochloride for treating neurogenic detrusor overactivity

Company/Developer	Farco-Pharma GmbH

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33502	NICE ID: 10751	UKPS ID: 662977

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Oxybutynin hydrochloride is in clinical development for the treatment of neurogenic detrusor overactivity (NDO), in patients managing bladder emptying by clean intermittent catheterisation. Damage to the spinal cord, via spina bifida, multiple sclerosis or injuries, can disrupt communication between the spinal cord and bladder causing NDO. NDO increases pressure in the bladder and decreases the volume of urine the bladder can hold, leading to unexpected and frequent urine leakage (urinary incontinence), increased urinary tract infection (UTIs) and vesicoureteral reflux. Treatment with oral anticholinergics are not effective in all NDO patients and are associated with substantial side effects.

Oxybutynin hydrochloride is a medicine that blocks some receptors in the body called muscarinic M1 and M3 receptors. In the bladder, this causes the muscles that push urine out of the bladder to relax. This leads to an increase in the amount of urine that the bladder can hold, and to changes in the way the bladder muscles contract as the bladder fills up, preventing unwanted urination. Oxybutynin hydrochloride is available as a tablet for the treatment of overactive bladder. This technology is a solution that can be administered directly to the bladder, reducing the side effects associated with oral administration. If licenced, oxybutynin hydrochloride as an intravesical application will provide a safe and effective treatment option for patients with NDO, in patients managing bladder emptying by clean intermittent catheterisation.

Proposed Indication

Treatment of detrusor overactivity due to spinal cord injury or myelomeningocele (spina bifida) in children from 6 years of age and adults, who are managing bladder emptying by clean intermittent catheterisation (CIC), not adequately managed with oral anticholinergics.[1]

Technology

Description

Oxybutynin hydrochloride (Vesoxx) has both direct antispasmodic action on the smooth muscle of the bladder detrusor muscle as well as anticholinergic action in blocking the muscarinic effects of acetylcholine on smooth muscle. These properties cause relaxation of the detrusor muscle of the bladder in patients with an unstable bladder. Oxybutynin hydrochloride increases bladder capacity and reduces the incidence of spontaneous contractions of the detrusor muscle.[2]

In the phase III clinical trial (2009-011843-38) patients were given intravesical application of 10 ml of 0.1% oxybutynin hydrochloride solution three times daily.[3,4] There are no fixed rules for the dose regimen as high interindividual differences in bladder pressure and doses required to improve neurogenic detrusor overactivity exist. The dose regimen (doses and timings) must therefore be determined individually according to the patient´s need. Individual dosages will be applied to control uro-dynamic parameters sufficiently (maximum detrusor pressure < 40 cm H_2O) aiming at complete inhibition of neurogenic detrusor overactivity.[5]

Key Innovation

Oral oxybutynin hydrochloride is one of the most commonly prescribed treatments for neurogenic detrusor overactivity (NDO) however, similar to other anticholinergic drugs, a major disadvantage of oral oxybutynin are the substantial side effects that result in treatment discontinuation. Conversely, there is evidence that the intravesical administration of oxybutynin hydrochloride results in less frequent and less intense side effects due to a reduced first-pass effect. After oral administration, plasma levels of the active metabolite N-desethyl-oxybutynin (N-DEO) are up to sevenfold higher compared to the parent compound, in contrast to a 1.2 ratio after intravesical administration, which likely explains the clinically relevant reduction of side effects following intravesical administration as N-DEO is also pharmacologically active.[3] As the first-pass effect is reduced, due to local application in the bladder, higher dosing is possible compared to systemic treatments.

If licenced, oxybutynin hydrochloride will provide a safe and effective treatment option for patients with NDO, in patients managing bladder emptying by clean intermittent catheterisation.

Regulatory & Development Status

Oral oxybutynin hydrochloride has Marketing Authorisation in the EU/UK for the following indications:[2]

- Treatment of frequency, urgency or urge incontinence as may occur in bladder overactivity whether due to neurogenic bladder disorders (detrusor hyperreflexia) or idiopathic detrusor overactivity in adults.
- Urinary incontinence, urgency and frequency in overactive bladder conditions caused by idiopathic overactive bladder or neurogenic bladder dysfunction (detrusor over activity) in children over 5 years.
- Nocturnal enuresis associated with detrusor over activity, in conjunction with non-drug therapy, when other treatment not been successful in children over 5 years.

Intravesically administered oxybutynin hydrochloride solution is already licenced in the UK for suppression of detrusor overactivity due to spinal cord injury or myelomeningocele (spina bifida) in children from 6 years of age and adults, who are managing bladder emptying by clean intermittent catheterisation, not adequately managed with oral anticholinergic.[1]

Patient Group

Disease Area and Clinical Need

NDO is a dysfunction of the bladder that results from congenital conditions (inherited conditions beginning at or before birth), such as spina bifida, or other disease or injury in the nervous system, such as spinal cord injury. With NDO, there is overactivity of the bladder wall muscle, which normally relaxes to allow storage of urine (detrusor muscle). The bladder wall muscle overactivity in NDO results in sporadic bladder muscle contraction, which increases pressure in the bladder and decreases the volume of urine the bladder can hold. If NDO is not treated, increased pressure in the bladder can put the upper urinary tract at risk of harm, including possible permanent damage to the kidneys. In addition, spontaneous bladder muscle contractions can lead to unexpected and frequent leakage of urine with symptoms of urinary urgency (immediate need to urinate), frequency (urinating more often than normal) and incontinence (loss of bladder control).[6] Urinary tract infections are a frequent complication of neurogenic bladder conditions such as NDO and may present with atypical signs and symptoms.[7] The literature suggests that health-related quality of life in patients with urinary incontinence due to NDO is worse than patients with urinary incontinence in general or those with the same underlying neurologic condition without urinary incontinence. In addition, urgency urinary incontinence also results in substantial economic costs.[8]

There are an estimated 50,000 people in the UK living with a spinal cord injury (SCI) and 90% of them suffer from neurogenic bladder, around 49.7% with detrusor overactivity.[9,10] The incidence of spina bifida is 0.06% of live births.[11] The rate of neurogenic bladder issues in people with spina bifida has been reported as over 95% but some studies have highlighted insufficient data.[9,12] An estimate of the spina bifida patients eligible for NDO treatment in the UK could not be obtained from available sources.

Recommended Treatment Options

NICE recommends antimuscarinic drugs to people with spinal cord disease (for example, spinal cord injury or multiple sclerosis) and symptoms of an overactive bladder such as increased frequency, urgency and incontinence.[13]

NICE recommends bladder wall injection with botulinum toxin type A to adults with spinal cord disease (for example, spinal cord injury or multiple sclerosis) and with symptoms of an overactive bladder and in whom antimuscarinic drugs (a subtype of anticholinergic drugs) have proved to be ineffective or poorly tolerated.[13]

Clinical Trial Information

Trial	**STEG-CORP_111804,** 2009-011843-38; Documentation of the efficacy and tolerability of intravesically applied oxybutynin solution in adult patients with detrusor hyperactivity caused by neurological disorder **Phase III -** Completed **Location(s):** Germany

	Primary completion date: November 2012
Trial Design	Randomised, parallel assignment, open label
Population	N = 36, detrusor hyperactivity confirmed and associated with a known neurological deficit, regularly perform clean intermittent catheterisation, aged 18 to 70 years
Intervention(s)	Intravesical application of 10 ml of 0.1% oxybutynin hydrochloride solution three times daily
Comparator(s)	Oral application of one tablet containing 5 mg oxybutynin hydrochloride three times daily
Outcome(s)	Primary outcome: • An alteration of the maximal cystometric bladder capacity between visit 1 and visit 3 (via urodynamic measurement) See trial record for full list of other outcomes.
Results (efficacy)	The increase in maximum bladder capacity was 117 ml with intravesical application (P =0.0002) versus 18 ml with the oral application (P =0.51). The difference was statistically significant (P =0.0086).[3]
Results (safety)	Adverse drug reactions (ADR) were reported by 10 (55.6% of) patients with intravesical administration, and by 14 (82.4% of) patients with oral administration. Significant differences in favour of the intravesical application were observed in ADR affecting vision (1/10 vs. 9/14), gastrointestinal tract (8/10 vs. 14/14), nervous system (2/10 vs. 8/14), and skin and subcutis (1/10 vs. 6/14). No serious adverse drug reactions were reported.[3]

Estimated Cost

The cost of intravesically administered oxybutynin hydrochloride solution is not yet known.

Relevant Guidance

NICE Guidance

- 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.[14]
- European Association of Urology. EAU Guidelines on Neurogenic Lower Urinary Tract Dysfunction. 2009.[15]

Additional Information

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