CDEC FINAL RECOMMENDATION

OXYBUTYNIN CHLORIDE GEL
(Gelnique – Watson Laboratories, Inc.)
Indication: Bladder, Overactive

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that oxybutynin chloride gel not be listed.

Reasons for the Recommendation:
1. The Committee considered the comparative clinical benefit of oxybutynin chloride gel to be uncertain because of the absence of any randomized controlled trials (RCTs) that directly compare it with other pharmacological treatments for overactive bladder.
2. There are no RCTs comparing the incidence of anticholinergic adverse effects (such as cognitive and neurological) between oxybutynin chloride gel and other oxybutynin products, particularly in the elderly.

Background:
Oxybutynin chloride gel has a Health Canada indication for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Oxybutynin chloride is an antispasmodic, anticholinergic agent. It is available as a topical gel formulation at a concentration of 100 mg/g, and the dose approved by Health Canada is 100 mg applied once daily.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of oxybutynin chloride gel, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients. The manufacturer submitted a confidential price for oxybutynin chloride gel.

Clinical Trials
The systematic review included one RCT of patients with a history of overactive bladder, with symptoms of urgency, urge urinary incontinence, and urinary frequency. Study OG05009 (N = 789) was a 12-week double-blind multi-centre trial, followed by a 14-week open-label safety period. Patients were randomized to either oxybutynin chloride gel 100 mg/g, 1 g applied

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once daily, or matching placebo. Both groups were trained in, and required to follow, non-pharmacological and lifestyle management interventions for overactive bladder.

Enrolled patients had an average duration of urinary incontinence of 102 months, and the majority of patients (89.2%) were female. The mean age was 59.4 years and 35.9% of patients were older than 65 years. At randomization, more than half of the included patients (56.4%) had more than four incontinence episodes per day.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: change in the number of (i) urge incontinence episodes, (ii) micturition events, and (iii) nocturia events; quality of life; serious adverse events; total adverse events; and withdrawal due to adverse events. The primary endpoint in study OG05009 was the change from baseline in the number of urge incontinence episodes per day

Quality of life was assessed using the Incontinence Impact Questionnaire and the King's Health Questionnaire. The Incontinence Impact Questionnaire is a 30-item questionnaire with four subscales: physical activity, travel, social and relationships, and emotional health. The total score ranges from 0 to 400 (0 to 100 for each subscale); higher scores reflect worsening impact. The King's Health Questionnaire includes 32 items that measure general health perception, incontinence impact, severity of urinary symptoms, and seven domains: role limitations, physical limitations, social limitations, personal relationships, emotions, sleep and energy, and severity (coping) measures. Scores range from 0 (best) to 100 (worst).

Results

Efficacy or Effectiveness

- Compared with placebo, oxybutynin-treated patients reported a statistically significantly greater reduction in the number of urge incontinence episodes per day; mean difference (MD) (95% confidence interval [CI]): –0.5 (–0.9 to –0.1).
- Compared with placebo, oxybutynin-treated patients reported a statistically significantly greater reduction in the number of micturition events per day; MD (95% CI): –0.7 (–1.12 to –0.28).
- The reduction in the number of nocturia events was not statistically significantly different between oxybutynin and placebo.
- Compared with placebo, oxybutynin-treated patients reported statistically significantly greater improvements in quality of life, as assessed by the total and subscale scores of the Incontinence Impact Questionnaire. There was no statistically significant difference between oxybutynin and placebo-treated patients on several domains of the King's Health Questionnaire, including general health perception, physical limitations, social limitations, and emotions.

Harms (Safety and Tolerability)

- The proportion of patients experiencing serious adverse events was not statistically significantly different between oxybutynin and placebo.
- The proportion of patients reporting an adverse event was statistically significantly higher in the oxybutynin group (56.8%) than in the placebo group (48.3%). The most commonly

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reported adverse events in the oxybutynin group were dry mouth, urinary tract infection, upper respiratory infection, and headache.

- The incidence of withdrawal due to an adverse event was similar between oxybutynin gel and placebo groups.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing oxybutynin chloride gel with other pharmacotherapies for overactive bladder approved in Canada (oxybutynin extended release [ER], oxybutynin immediate release [IR] oxybutynin chloride ER patch, tolterodine ER, trospium chloride, solifenacin succinate, and darifenacin) based on the assumption of similar clinical efficacy. The manufacturer considered the costs of managing adverse events in its analysis, using a naive indirect comparison of information reported in product monographs. The manufacturer's cost-minimization analysis was limited by the lack of evidence to support similar clinical effects and comparative information on adverse events (e.g., a lack of head-to-head RCT or formal indirect comparison).

At the submitted confidential price, the daily cost of oxybutynin chloride gel (*[confidential price removed at manufacturer's request]*) is similar to that of oxybutynin chloride ER patch ($1.80); is less expensive than oxybutynin ER ($1.79 to $5.36) and tolterodine and tolterodine ER ($1.85); and is more expensive than trospium chloride ($1.53), solifenacin ($1.50), darifenacin ($1.46), and oxybutynin IR ($0.20 to $0.39). The confidential price was used by the Committee in making the listing recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Patient Input Information:

The following is a summary of information provided by one patient group that responded to the CDR Call for Patient Input:

- Urinary incontinence associated with overactive bladder can have a significant impact on the physical, social, and emotional health of affected persons.
- Side effects associated with the available formulations of anticholinergic medications, particularly dry mouth, are reported to be a major cause of patient non-adherence and treatment discontinuation.

Other Discussion Points:

- The Committee discussed that anticholinergic effects of overactive bladder treatments are of particular concern in the elderly, and that a product with fewer anticholinergic adverse effects compared with available treatments would represent an advance.
- The Committee considered the possibility of recommending listing oxybutynin chloride gel for patients who cannot tolerate or have insufficient response to an adequate trial of immediate-release (IR) oxybutynin. However, in addition to the lack of active comparator trials, no RCTs provide data specific to this patient population; a manufacturer provided subgroup analysis of previous or current users of overactive bladder medications from study OG05009 did not address this shortcoming.
- The Committee noted that non-pharmacological measures (e.g., fluid management, Kegel exercises, and decreasing exposure to bladder irritants) are an important component in the management of overactive bladder.

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CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

March 21, 2012 Meeting

Regrets:
None

Conflicts of Interest:
None

May 16, 2012 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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