CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

GLYOPYRROLATE ORAL SOLUTION (CUVPOSA — Medexus Pharmaceuticals, Inc.)
Indication: Chronic severe drooling, neurologic (pediatric).

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that glycopyrrolate oral solution not be reimbursed to reduce chronic severe drooling in patients aged three to 18 years with neurologic conditions associated with problem drooling.

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Reasons for the Recommendation

1. CDEC reviewed one phase III randomized controlled trial (RCT) comparing glycopyrrolate with placebo (Study FH-00-01). Although the results of this RCT suggested that treatement with glycopyrrolate reduced the degree of drooling in some patients (measured using the modified Teacher's Drooling Scale [mTDS]) compared to treatment with placebo, it is unclear whether the changes observed in drooling represent a clinically meaningful improvement. Specifically, the mTDS is a subjective, unvalidated scale and no information pertaining to the minimal clinically important difference (MCID) for the mTDS was identified in the literature.
2. CDEC determined that it was unlikely that the results of Study FH-00-01 are generalizable to patients routinely seen in clinical practice in Canada. The patients included in the study may not be reflective of children with chronic, severe drooling in Canada. Study FH-00-01 mainly included patients with cerebral palsy (75% and 70% of patients in the glycopyrrolate and placebo groups, respectively). Up to 50% of patients with cerebral palsy have coexisting seizure disorders but only one patient in the placebo group had an underlying neurologic condition that may have included epilepsy. Study FH-00-01 excluded patients who had poorly controlled seizures (defined as daily seizures). Anticholinergic drugs, such as glycopyrrolate, can lower the seizure threshold. Given that glycopyrrolate may be prescribed in patients with coexisting seizure disorders, the impact of this drug on seizure control is a critically important outcome, which was not available in the study under review.
3. There are no comparative studies of glycopyrrolate versus other treatment options used in Canada to reduce severe drooling, including botulinum toxin, other anticholinergic drugs (atropine, benztropine, trihexyphenidyl), and surgical interventions. Therefore, the comparative effectiveness and safety of glycopyrrolate compared with other treatment options is unknown.
4. A high proportion of adverse effects were observed in Study FH-00-01. All 20 patients treated with glycopyrrolate experienced adverse events (AEs), of whom eight patients (40%) had mild AEs, seven (35%) had moderately severe events, and five (25%) had severe AEs. Gastrointestinal and respiratory AEs were more common in patients treated with glycopyrrolate than with placebo, which may have led to unblinding.
5. Study FH-00-01 was only eight weeks long, which is insufficient to determine the long-term efficacy and potential AEs of treatment for a chronic condition such as severe drooling. Therefore, the long-term safety and efficacy of glycopyrrolate are unknown.

Discussion Points

1. The blood-brain barrier may have lower permeability to glycopyrrolate compared with other anticholinergic drugs, which may increase tolerability for patients with central nervous system impairment. However, the potential reduction in anticholinergic AEs associated with glycopyrrolate has not been demonstrated.
2. CDEC discussed that it may be difficult to assess adverse responses in children who are neurologically impaired and have significant difficulties expressing their response to medications.

Background

Glycopyrrolate has a Health Canada indication to reduce chronic, severe drooling in patients three to 18 years old with neurologic conditions associated with problem drooling (e.g., cerebral palsy). Glycopyrrolate is a synthetic quaternary ammonium anticholinergic drug that does not easily cross the blood-brain barrier. Glycopyrrolate inhibits the action of acetylcholine on salivary glands, thereby reducing the extent of salivation. It is available as an oral solution (1 mg/5 mL), with each mL containing 0.2 mg of glycopyrrolate. The Health Canada–recommended dosage is to initiate glycopyrrolate oral solution at 0.02 mg per kg of body weight three times

daily and titrate in increments of 0.02 mg/kg every five to seven days based on therapeutic response and adverse reactions. The maximum recommended dosage is 0.1 mg/kg three times daily, not to exceed 1.5 mg to 3 mg per dose based on weight.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of one RCT of glycopyrrolate oral solution and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating pediatric patients with chronic, severe drooling.

Summary of Patient Input

No patient group input was received for this review.

Clinical Trials

One phase III RCT was included in the systematic review. FH-00-01 (N = 38) was a multi-centre, randomized, double blind, placebo-controlled, eight-week study conducted at multiple sites in the US and was designed to assess the safety and efficacy of oral glycopyrrolate liquid (1 mg per 5 mL) compared with placebo in the management of problem drooling in children with cerebral palsy or other neurologic conditions. Patients enrolled in this study were those between three and 16 years of age who exhibited severe drooling. They were randomized in a 1:1 ratio to either glycopyrrolate or placebo. The dose of glycopyrrolate was titrated during the first four weeks of the study. The primary outcome was the treatment responder rate based on the mTDS at week 8 (the change in mTDS score from baseline to week 8 was also reported). Secondary outcomes included responders and change from baseline on the mTDS at weeks 2, 4, and 6, and patient/caregiver and physician global assessments. A total of five patients withdrew from the study prematurely (two patients in the glycopyrrolate group and three patients in the placebo group).

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review (CDR) systematic review protocol. Of these, the committee discussed the responder rate and change from baseline on the mTDS and global assessments.

The primary outcome in Study FH-00-01 was the difference in responder rate based on the mTDS. Responders were defined as those showing at least a three-unit improvement on the mTDS. The mTDS is a nine-point subjective scale categorizing severity and frequency of drooling. The scale ranges from "1" (dry; never drools) to "9" (profuse frequent drooling, with clothing, hands, tray, and objects becoming wet). Although it has been used in clinical studies for the assessment of drooling, the mTDS is not a validated scale. No information pertaining to the MCID for the mTDS was identified in the literature, though the FDA recognizes a three-unit change on the mTDS as being indicative of a treatment responder.

Global assessments were conducted by physicians, caregivers, and patients with sufficient intellectual capacity. The global assessment is a five-point scale (1 = strongly agree; 2 = agree; 3 = neutral; 4 = disagree; 5 = strongly disagree) applied to the statement, "This is a worthwhile treatment." Global assessment was conducted at week 8 or at study discontinuation. No information pertaining to the MCID for the global assessment was identified in the literature.

Efficacy

In Study FH-00-01, the responder rate based on the mTDS at week 8 was statistically significantly higher for the glycopyrrolate group (47%) than for the placebo group (6%; $P = 0.004$). Further, statistically significantly more glycopyrrolate-treated patients were classified as responders at weeks 2, 4, and 6 compared with placebo-treated patients. In addition, mean improvements in change from baseline at week 8 were statistically significantly greater in the glycopyrrolate group than in the placebo group (–3.5 versus –0.1; $P = 0.019$).

Health-related quality of life was not measured in Study FH-00-01; however, treatment satisfaction was assessed at week 8 using caregiver and physician global assessment and was a secondary end point. Nineteen (100%) parents or caregivers of glycopyrrolate-treated patients versus nine (56%) parents or caregivers of placebo-treated patients agreed that the treatment was "worthwhile" ($P =$

0.002). Similarly, 16 (84%) physicians in the glycopyrrolate group versus seven (41%) in the placebo group agreed that the treatment was “worthwhile” (*P* = 0.014). However, none of the secondary outcomes in Study FH-00-01 were adjusted for multiplicity, and no information pertaining to the MCID for the global assessment was identified in the literature.

Reduction in salivary production and reduction in unwanted symptoms were also identified as efficacy outcomes of interest in the CDR systematic review protocol; however, these outcomes were not assessed in the clinical trial included in this review.

Harms (Safety)

In Study FH-00-01, all 20 patients treated with glycopyrrolate experienced AEs, of which eight patients (40%) had mild AEs, seven (35%) had moderately severe AEs, and five (25%) had severe AEs. Of these severe AEs, the most common was constipation, which was reported in 15% of patients. Sixteen patients (89%) in the placebo group experienced AEs, and all were mild or moderate in severity. The most common AEs were gastrointestinal in nature: constipation, diarrhea, vomiting, and dry mouth. SAEs occurred infrequently. One patient in the glycopyrrolate group experienced one SAE of generalized tonic-clonic seizure activity followed by generalized convulsions post-treatment. No deaths were reported in Study FH-00-01.

Gastrointestinal and respiratory AEs were identified as notable harms of interest. Seventeen patients (85%) in the glycopyrrolate group reported gastrointestinal events, while nine patients (50%) in the placebo group reported gastrointestinal events. The most common gastrointestinal complaints in the glycopyrrolate and placebo groups, respectively, were constipation (seven [35%] versus three [17%]), diarrhea (three [15%] versus four [23%]), vomiting (eight [40%] versus two [11%]), and dry mouth (eight [40%] versus two [11%]). Respiratory AEs were reported by nine patients (45%) in the glycopyrrolate group and five patients (28%) in the placebo group. Nasal congestion was the most common respiratory AE reported.

Indirect Treatment Comparisons

No indirect evidence was submitted by the sponsor. An independent literature search for indirect evidence conducted by CADTH did not identify any evidence that met the inclusion criteria of the CDR review protocol.

Cost and Cost-Effectiveness

Glycopyrrolate oral solution is available in a 1 mg/5 mL concentration in 473 mL bottles at a submitted price of $625 per bottle, or $6.61 per mL. The recommended starting dosage of glycopyrrolate is 0.02 mg/kg three times daily, titrated in increments of 0.02 mg/kg every five to seven days based on therapeutic response and adverse reactions. The maximum recommended dosage is 0.1 mg/kg three times daily, not to exceed 1.5 mg to 3 mg per dose. For a 30 kg patient, depending on dose, the daily cost of glycopyrrolate at the submitted price ranges from $11.98 to $59.46.

The sponsor submitted a cost-utility analysis comparing glycopyrrolate oral solution with no treatment in patients three to 18 years old with neurologic conditions associated with problem drooling from the perspective of a Canadian publicly funded health care system over a 24-week time horizon. The model structure was a decision tree in which patients in each group entered the model according to their baseline distribution of mTDS scores as observed in Study FH-00-01. The model allowed for a single transition in mTDS score at two weeks, which was based on the mTDS distribution of scores observed in the clinical trial at eight weeks. Utility values were based on mTDS score where the utility of cerebral palsy without drooling was assigned a value of 0.500, and each one-point increase in mTDS score was assigned a disutility of 0.025. AEs were not considered. Only drug acquisition costs were included in the model, with dosage based on body weight. Patient age was sampled from a uniform distribution within the indicated age range of three to 18 years, and patients were assumed to have weights consistent with the 50th percentile from World Health Organization growth charts for Canada.

CADTH identified a number of key limitations with the model submitted by the sponsor:

1. Active comparators such as botulinum toxins were not considered.
2. The model was overly simplistic, including only a single transition point for treatment response without the possibility of further improvement, loss of response, or treatment discontinuation.
3. The time horizon was insufficient to assess the impacts of treatment for a chronic condition.

4. The time point at which patients experienced benefits from glycopyrrolate within the model was not consistent with the time point at which it was measured within the FH-00-01 trial.
5. The disutility of 0.025 for each point of mTDS score was arbitrary (i.e., based on 5% of the utility assigned to the least severe state [0.5]).
6. The analysis should be conducted on an identical population for each treatment group. Baseline mTDS score differed between patients receiving glycopyrrolate and no treatment, affecting the ability to make a fair comparison.
7. The modelled age distribution was not consistent with FH-00-01, and patient weight was overestimated for the population modelled.
8. AEs were inappropriately excluded from the model.

CADTH attempted to address some of the identified limitations by incorporating efficacy at a time point consistent with when it was measured in Study FH-00-01 (four weeks); applying the pooled baseline mTDS score distribution to both groups; adjusting patients' age distribution to be consistent with that of FH-00-01; and assuming patients' weight to be at the 25th percentile of Canadian growth charts.

Based on these revisions, the CADTH reanalysis resulted in an incremental cost-effectiveness ratio of $292,274 per quality-adjusted life-year. In order to be considered cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year, a price reduction of 83% would be required for glycopyrrolate. CADTH notes that these results are highly uncertain due to the number of limitations with the model structure that could not be addressed in the reanalysis. The cost-effectiveness of glycopyrrolate relative to the active comparators currently used in Canada is unknown, as is its cost-effectiveness beyond 24 weeks.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

November 20, 2019 Meeting (Initial)

Regrets

None

Conflicts of Interest

None

June 17, 2020 Meeting (Reconsideration)

Regrets

None

Conflicts of Interest

None