COST-EFFECTIVENESS OF GLYCOPYRRONIUM BROMIDE ORAL SOLUTION FOR THE MANAGEMENT OF SEVERE SIALORRHEA IN CHILDREN WITH CEREBRAL PALSY IN POLAND

ACCEPTANCE CODE:
EE740

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INTRODUCTION

Chronic sialorrhea is certainly one of the major inconveniences of daily life for children and adolescents burdened with neurological disorders. Cerebral palsy is one of the most common cause of sialorrhea, an unintentional loss of saliva from the mouth considered pathological if present after 3 years of age. Sialorrhea strongly affects the quality of life of young patients, exposing them to stigmatization by their peers, as well as severely burdening their caregivers. Chronic sialorrhea is further associated with the risk of secondary bacterial or fungal infections, ending with the dangerous aspiration of saliva into the lungs[1,2].

Uncontrolled drooling, combined with the neurological disorders present, puts a significant health burden on the patient, including both physical and psychological aspects, which directly translate into a reduced quality of life for the patients, which can become worse as the disease progresses.

The lack of a preparation suitable for children, approved for the treatment of sialorrhea, is currently an obstacle to the effective treatment of this disorder[3].

In Poland, according to experts, no treatment to reduce sialorrhea is currently used in the analyzed target population. Consequently, there is a great unmet need, and the choice of comparator is limited to the lack of treatment.

Glycopyrronium bromide, as a drug from the muscarinic receptor inhibitor group with a positive safety profile and high efficacy, addresses the unmet therapeutic need in the analyzed patient population[4,5,6].

OBJECTIVES

The objective is to assess the cost-effectiveness of a novel liquid formulation of glycopyrronium bromide (GLI), for the management of severe sialorrhea in children and adolescents aged 3 years and older with cerebral palsy in Poland.

A systematic review of economic analyses was performed for the target population.

The database search for this review was performed on the 7th of September, 2023.

No economic analyses were found that accurately matched the defined inclusion criteria related mainly to the target population, comparator, the pharmaceutical form of glycopyrronium bromide and the utility cost analysis performed. Therefore, the analysis also decided to include analyses for a broader population that also included adult patients with severe sialorrhea and neurological disorders, as well as patients using other therapies to treat severe sialorrhea (CADTH 2020[7], Langham et al. 2017[8], Makino et al. 2020[9], NICE TA605[10], NICE ES5[11] and NICE NG62[12]). Some of these economic analyses were used to build the economic model.

Studies were screened for inclusion based on titles/abstracts, and then full text, by two independent authors.

METHODS

A Markov model was built considering 5 mutually exclusive heath states to perform a cost-utility analysis comparing glycopyrronium bromide with no treatment.

The model consisted of a hypothetical cohort of patients transiting between severity-based health states, defined according to the Drooling Severity and Frequency Scale (DSFS), in 2-weekly cycles over 1 year.

Figure 1. Structure of the model included in the economic analysis (up to and including week 8 of treatment)

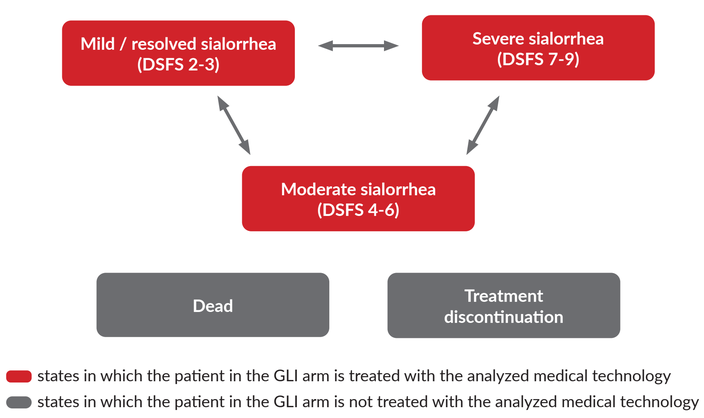
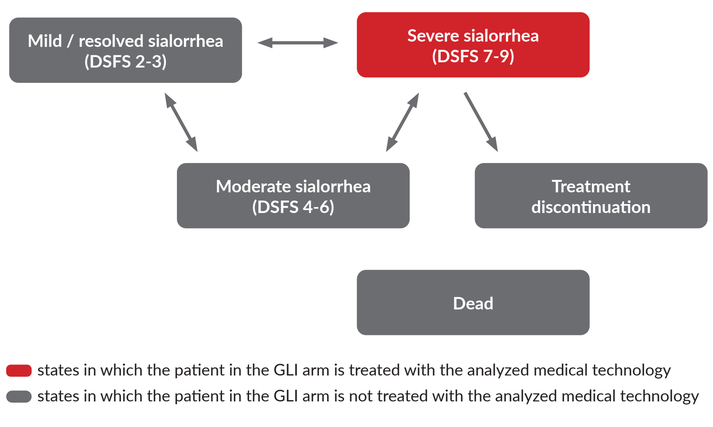


Figure 2. Structure of the model included in the economic analysis (after 8 weeks of treatment)



1. **Severe sialorrhea (DSFS 7-9)** - entry state; in this state, patients in the GLI arm receive treatment with glycopyrronium bromide; discontinuation of treatment in the GLI arm occurs when severe side effects appear or after the 24th week of treatment in patients who do not respond to treatment (they have been in the severe sialorrhea state since the start of treatment) - whichever comes first;
2. **Moderate sialorrhea (DSFS 4-6)** - in this state, patients in the GLI arm take the drug up to and including week 8 (from the start of treatment), and then discontinue treatment due to the high ratio of risk of adverse events to health benefits;
3. **Mild sialorrhea/resolved sialorrhea (DSFS 2-3)** - in this state, patients in the GLI arm use the drug up to and including week 8 (from the start of treatment) and then discontinue treatment due to the high risk ratio of adverse events to health benefits;
4. **Discontinuation of treatment** - caused by factors other than improvement on the DSFS scale, including the occurrence of severe adverse events and long-term non-response to treatment; does not apply to the no-treatment arm, in which patients do not use glycopyrronium bromide;
5. **Death** - absorbing state.

The efficacy and distribution of patients between sialorrhea severity states were modeled using a placebo-controlled randomized trial (Zeller et al. 2012[13]) and a single-arm clinical trial (Zanon et al. 2021[14]). In order to use the results from studies available at different scales (mTDS and DSFS), a mapping of the mTDS scale to the validated DSFS scale was carried out. The sensitivity analysis also tested the inclusion of data from other clinical trials (Zeller et al. 2012[15], Mier et al. 2000[16]).

A systematic review was conducted to estimate quality of life for each condition considered in the model. Finally, data from NICE publications TA605[10] and NICE NG62[12] were used in the primary analysis. The following relation of quality of life to DSFS scale values was used:

$$QoL(DSFS) = -0.0425 \times DSFS + 0.6408,$$

based on which quality of life values were estimated for the health states (as the quality of life value for the middle of the DSFS range in a given health state). In the state of discontinuation of treatment, it was assumed that the quality of life of patients returns to the baseline, which is the state of severe sialorrhea, so the quality of life in this state is the same as in the state of severe sialorrhea.

The sensitivity analysis tested the inclusion of data from other publications found (Makino et al. 2020[9], Chang et al. 2012[17]).

Table 1. Utility input in the baseline analysis

HEALTH STATE	UTILITY	SOURCE
Severe sialorrhea (DSFS 7–9)	0.3008	NICE TA605[10], NICE NG62[12]
Moderate sialorrhea (DSFS 4–6)	0.4283	
Mild/resolved sialorrhea (DSFS 2–3)	0.5346	
Baseline/Discontinued patients	0.3008	Assumption

Key: DSFS, Drooling Severity and Frequency Scale

Only direct healthcare costs were considered from the public payer perspective using local Polish NHS tariffs [18,19]. The following cost categories incurred from a public payer perspective were considered and evaluated:

- drug costs;
- costs of prescribing and administering drugs;
- monitoring costs;
- costs of adverse events.

Table 2. Included costs per model cycle (PLN)

RESULT CATEGORY	GLYCOPYRRONIUM BROMIDE	NO TREATMENT
Public payer perspective		
Differential cost of drugs	1 950.64	0,00
Differential cost of administration/ prescription of drugs	12.50	0.00
Differential cost of treating adverse events	3.52	0.00
Differential cost of monitoring	37.50	0.00
Total differential cost	2 004.16	0.00

The primary outcome measure was the incremental cost-effectiveness ratio (ICER), representing cost per quality-adjusted life-year (QALY). Probabilistic and deterministic sensitivity analyses were conducted.

RESULTS

The use of glycopyrronium bromide is associated with specific and significant health benefits, which include the generation of additional quality-adjusted life years and a reduction in the severity of patients' sialorrhea.

The analysis further showed that the use of GLI, rather than no treatment, generates higher costs, due to the cyclical cost of therapy with the drug glycopyrronium bromide.

Table 3. Results of utility cost analysis

RESULT CATEGORY	PUBLIC PAYER PERSPECTIVE
INCREMENTAL HEALTH EFFECT	
Incremental total QALY	0.08
INCREMENTAL COST (PLN)	
Incremental total cost differential of compared therapies	13 604.55
Incremental cost differential of glycopyrronium bromide	13 005.05
Incremental cost differential of drug administration	106.64
Incremental cost differential of adverse events	92.01
Incremental cost differential of monitoring	400.86
ICUR (PLN/QALY)	
ICUR	**174 524.90**

Key: QALY, quality-adjusted life-year; PLN, Polish Zloty; ICUR, incremental cost-effectiveness ratio

Compared to no treatment, glycopyrronium bromide generated 0.08 QALY at an additional cost of PLN 13,604.55. ICER was estimated at 174,524.90 PLN per QALY and was below the applicable willingness to pay threshold of PLN 190,380/QALY[20]. The wide variety of sensitivity and scenario analyses performed showed that the cost-effectiveness results were sensitive to some of the model inputs, including baseline age, utility values, dosing and the possibility of treatment discounting.

Figure 3. Scenarios and parameters of sensitivity analysis that cause the greatest changes in ICUR values

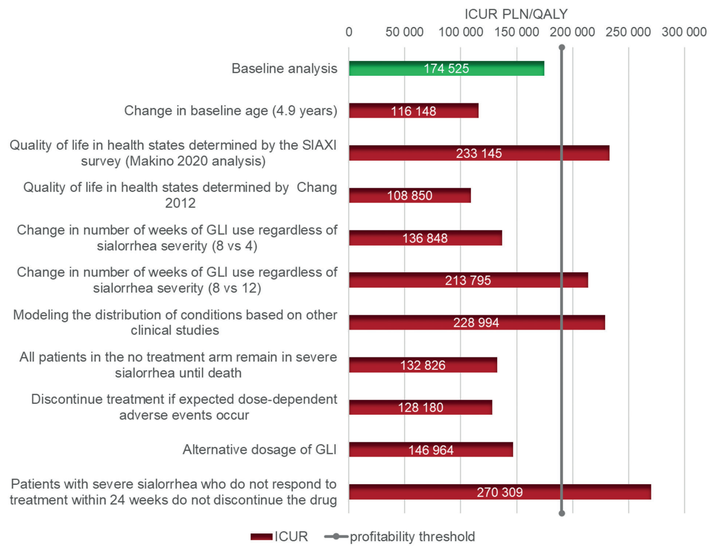
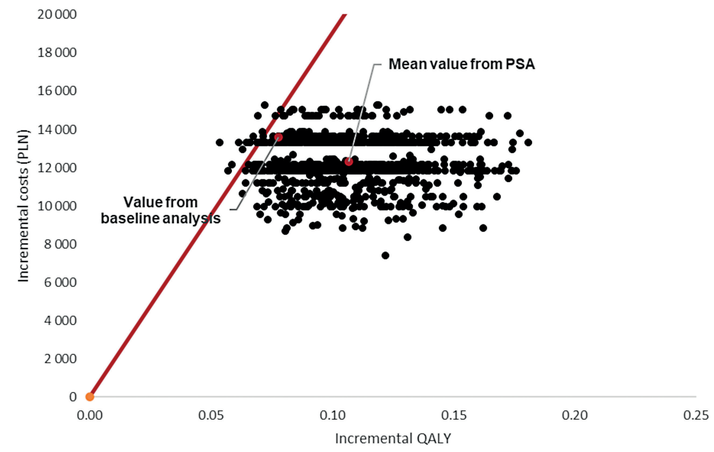


Figure 4. Results of probabilistic sensitivity analysis



The results of the probabilistic sensitivity analysis presented above indicate that the baseline variant of the analysis was conducted for conservative values of the input parameters. The average results of the probabilistic sensitivity analysis indicate a better result of the analysis.

The probability that the technology will be cost-effective (below the cost-effectiveness threshold of PLN 190,380/QALY) for the medical technology under review is about 98% from a public payer perspective.

LIMITATIONS

- The main limitation is related to basing the analysis for comparing the evaluated medical technology with a comparator on a compilation of data from various available clinical trials (including single-arm trials).
- It was assumed that the patient would stop using glycopyrronium bromide after at least 8 weeks from the start of use if he or she achieved improvement in the severity of sialorrhea.
- In the baseline analysis, it was assumed that a patient stops using glycopyrronium bromide after 24 weeks of treatment if they have been in a state of severe salivation since the start of treatment and have not responded to treatment.
- No evidence was found of the effect of glycopyrronium bromide on the course of specific neurological disorders (i.e. cerebral palsy); it was assumed that the cost of their treatment is invariant to treatment with GLI or a comparator.
- In determining quality of life values (for the included health states), values from the TSG scale were adjusted to match the scores of the validated DSFS scale, according to the methodology described in NICE publication TA605.

CONCLUSIONS

Treatment with glycopyrronium bromide is the first therapy dedicated to children and adolescents, aged 3 years and older, with severe sialorrhea in cerebral palsy in Poland.

The analysis showed that glycopyrronium therapy is cost-effective compared to the comparator (no treatment). The cost of an additional year of quality-adjusted life gained with glycopyrronium bromide instead of the comparator is lower than the applicable cost-effectiveness threshold (PLN 190,380/QALY).

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