Health Policy and Technology 8 (2019) 84–91

Contents lists available at ScienceDirect

Health Policy and Technology

journal homepage: www.elsevier.com/locate/hlpt

Cost-utility analysis of cariprazine compared to risperidone among patients with negative symptoms of schizophrenia

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ARTICLE INFO

Article history:
Available online 31 January 2019

Keywords:
Schizophrenia
Cariprazine
Health economic modelling
Cost-utility analysis
Hungary

ABSTRACT

Objectives: The aim was to assess the cost-effectiveness of cariprazine compared to second-generation antipsychotics in the treatment of schizophrenia for patients with negative symptoms in Hungary.
Methods: To assess the cost-effectiveness of cariprazine, a deterministic 8-health state Markov cohort model was built. The analysis was performed from a third-party payer perspective. Data were gathered from relevant sources of the scientific literature and public databases. Unit costs were based on tariffs of the National Health Insurance Fund Management. Key assumptions on treatment pathways and resource utilization were supported by experts to reflect clinical practice. These assumptions include the option of therapy switching, and selection of a 2-year time horizon. Deterministic and probabilistic sensitivity analyses were also conducted, together with scenario analyses.
Results: The use of cariprazine resulted in 1.45 Quality-Adjusted Life Years (QALY) per patient, and a total cost of 3340 Euros per patient over a time horizon of 2 years. The use of risperidone resulted in 1.40 QALY/patient, and a total cost of 1896 Euros per patient. The incremental cost-effectiveness ratio (ICER) of the comparison between cariprazine and risperidone is therefore 28,897 Euros/QALY. The sensitivity analyses and the scenario analysis confirmed the robustness of the base-case results.
Conclusions: Cariprazine compared to risperidone in the treatment of schizophrenia for patients with negative symptoms provides additional health gain at acceptable costs according to the willingness to pay threshold in Hungary. The findings of the analysis were proven to be robust in the scenario analyses and sensitivity analyses.

Introduction

Schizophrenia is considered to be one of the major health issues in psychiatry. It imposes high health, social, and economic burden, not only on patients but also on families, caregivers, and the wider society [1]. It significantly increases mortality and decreases life expectancy as well [2]. The prevalence of schizophrenia ranges from four to seven per 1000 persons worldwide [3]. The annual prevalence was estimated between 0.51% and 0.53% in the USA [4] and 0.31% in Western Europe [5], while the median lifetime prevalence was 0.4% in the US [6].

Patients with schizophrenia are often divided into subgroups based on the presence of positive or negative symptoms of the disease [7]. Patient response to medications with negative symptoms of schizophrenia is generally limited [8]. As reported by Németh and colleagues [9], treatment of patients with negative symptoms of schizophrenia with the novel substance of cariprazine can address this unmet need.

In the randomised, double-blind, controlled clinical trial, cariprazine showed a significant difference in effects compared to risperidone both in the primary and the secondary endpoints [9].

The primary endpoint was defined as the change from baseline to week 26 or end of treatment on the Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS). The Positive and Negative Syndrome Scale (PANSS) is considered to be the most commonly used standardised questionnaire for assessing the symptoms of schizophrenia [10], being a 30-item scale with seven Positive symptom subscale (POSS) items, seven Negative symptom subscale (NEGS) items and sixteen General Psychopathology subscale items [11]. With this structure, PANSS can be considered especially relevant for assessing specific symptoms, as for example negative symptoms, observing the changes experienced

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https://doi.org/10.1016/j.hlpt.2019.01.004
2211-8837/

Table 1
Key assumptions of the cost-effectiveness calculations.

Assumption	Rationale
The cost-effectiveness of schizophrenia in the treatment of patients with negative symptoms of schizophrenia can be adequately conducted by using the 8 Mohr–Lenert health states as a framework	The Mohr–Lenert approach [12–15] is a widely known categorization of patients with schizophrenia. It captures both the severity and the type of the symptoms of schizophrenia. Both utilities and Western European resource use data [16] associated with these eight health states is available from scientific publications.
Medication adherence and persistence was not included in the current model	The double-blind randomized controlled clinical trial could not deliver adequate information about adherence or persistence under real-life circumstances, and the scientific literature did not provide links to the Mohr–Lenert health states either. As a conservative approach only therapy switching was implemented in the current version of the model.
Therapy switching in the models is based on the comprehensive data published by Lieberman et al. on reasons of discontinuation of risperidone treatment.	No evidence from the scientific literature was available describing switching rates related to Mohr–Lenert health states. The approach of Lieberman et al. [23] takes into account several factors: switching due to lack of efficacy, switching due to adverse events, and switching due to decision of the patient and other reasons.
Adverse events were assumed not to be dependent on health state	Due to the lack of data on the link between adverse events and Mohr–Lenert health states, this conservative approach was taken.
Neither disease specific nor health state specific mortality was assumed	As the clinical trial, that served as the basis of the analysis, provided no data on mortality in connection with the 8 Mohr–Lenert health states, this conservative approach was taken.
The gaps of transitional probability matrices needed to be filled	In order to model the real-world situation the matrices had to be completed, and we had to look for the best available evidence in the form of expert interviews. In order to minimise uncertainty, the conservative choices were made to use the same data from the expert interviews on both the cariprazine arm and the comparator arm, and to assign the lowest possible weight to the data from the expert interviews.
Time horizon was chosen to be adjustable between 1 year and 10 years	Based on a systematic literature review on health economic models developed for schizophrenia [34], the majority of Markov cohort or Patient-level simulation models had time horizons between these two values.

by patients over time. Total PANSS scores can also be divided into five factor scores (Positive, Negative, Cognitive, Mood, and Hostility Factor Scores) [12]. Similarly to the result of the primary endpoint, where the effect of cariprazine was significantly greater than the effect of risperidone, results were confirmed by the secondary endpoint, where the total Personal and Social Performance (PSP) scale score was the efficacy parameter [9]. The clinical trial showed no association between severity of the disease and mortality [9].

With respect to the clinical benefits of cariprazine, our study aims at assessing its cost-effectiveness compared to risperidone and other second-generation antipsychotics in the treatment of patients with negative symptoms of schizophrenia in Hungary.

Methods

Structure of the Markov model

To assess the cost-effectiveness of cariprazine, a deterministic 8-health state Markov cohort model was built. The structure follows the eight schizophrenia health states developed by Mohr and Lenert [12–15], taking into account not only the severity of the symptoms, but the disease types as well (i.e. positive, negative, cognitive). The structure was confirmed by the availability of the utility values associated with these eight health states [13], as well as healthcare resource use data from three Western European countries [16]. The structure of the 8 state Markov model was previously published by Németh et al. [17]. The key assumptions of this analysis are included in Table 1.

Comparator choice

Risperidone was used as a comparator in the base-case analysis, due to the availability of the direct clinical comparison with cariprazine [9]. As risperidone has the lowest therapeutic cost per day in Hungary compared to all the reimbursed antipsychotic products [18], the choice of comparator was in line with the instructions of the current Hungarian health economic guideline [19]. As a scenario analysis, the model compares cariprazine with olanzapine, the most frequently used second-generation oral antipsychotic.

Patient population and treatment pathways

The patient population was defined as a reflection of patients with negative symptoms of schizophrenia in the RGH-188-005 clinical trial [9]. The average age of patients (40 years), as well as the proportion of genders (percentage of males and females), were similar to the clinical trial population. The patient cohort in the model starts from the Mohr–Lenert health states 4 (50%) and 6 (50%), being the typical health states for patients with negative symptoms. Weekly cycles for the initial 6-week period and 12-week cycles for the latter periods were chosen as appropriate periods to model costs and benefits. Two pairs of transition probability matrices were used for cariprazine and for its comparator: one for the first 6 weeks and one for the rest of the modelled time horizon. The detailed process of calculating transition probabilities based on clinical trial data and expert interviews were reported elsewhere [20]. As the efficacy of second-generation antipsychotics was assumed not to differ significantly [21], the transition probability matrices of risperidone were used in the scenario analysis when olanzapine was the comparator of cariprazine. The transition probability matrices are presented in the Appendix.

To model the real-life behaviour of patients, therapy switching due to adverse events [22] and disease progression using the evidence on concomitant medication use were considered [23]. Based on the clinical trial results reported by Németh et al. [9] the following adverse events were considered: akathisia, dyskinesia, orthostatic hypotension, Parkinsonism and pseudo-Parkinsonism, sedation and somnolence and clinically significant weight gain. For the base case analysis, the model was set to follow patients over a time horizon of 2 years to at most the time of death, to assess the relevant clinical and economic aspects of the cariprazine therapy; other periods were tested in the sensitivity analysis.

Input data

Input parameters were derived from the scientific literature, clinical trial data and publicly available data sources. Structured in-depth interviews with two clinicians having decades of experience treating patients with schizophrenia were used to validate

Table 2
Cost inputs of the cost-effectiveness model.

Cost data	Value in HUF	Value in EUR	Data source
Risperidone daily cost	20.35	0.07	[18]
General practitioner visit	1448	4.67	[27]
Psychiatrist visit	4270.2	13.76	[24–26]
Psychologist/professional nurse visit	1326.6	4.28	[24–26]
Hospitalization daily cost	16,488.8	53.15	[24–26]

EUR = Euros; HUF = Hungarian Forints.

Table 3
Cost inputs of adverse events.

Adverse event	Resource use			
	Visit type, unit	Reimbursed drug in use	Drug cost (Amount of reimbursement)	
			Value in HUF	Value in EUR
Dyskinesia	1 psychiatrist visit	–	–	–
Pseudo-parkinsonism	1 psychiatrist visit	Akineton 2 mg tablet 50x	768	6.8
akathisia	1 psychiatrist visit	Akineton 2 mg tablet 50x	213	0.7
Orthostatic hypotension	1 psychiatrist visit	–	–	–
Sedation and somnolence	1 psychiatrist visit	–	–	–
Clinically significant weight gain	1 general practitioner visit	–	–	–

EUR = Euros; HUF = Hungarian Forints.

data and key assumptions. In line with the instructions of the current Hungarian health economic guideline [19], the inputs were calculated from the third-party payer perspective.

(a) Costs

For the base-case analysis direct medical costs were considered. Resource use of patients with schizophrenia was derived from the results of the European Schizophrenia Cohort (EuroSC) [16]. Unit cost data of hospitalization, psychiatrist visits, psychologist (professional nurse) visits, and visits of general practitioner (GP) are based on the Hungarian tariffs of the National Health Insurance Fund Management (NEAK) in year 2017, published by the Hungarian Ministry of Health [24–27]. Costs of risperidone and olanzapine were extracted from the tariff tables of the NEAK [18], while cariprazine daily costs were not disclosed at the time of the submission of this manuscript. Data collection was supported by expert interviews in order to assure that the costs included in the model reflect the costs in practice. Cost inputs are presented in Table 2.

The most frequently used Diagnosis-related Group codes and their values in Hungarian Forints [24–26], and the most frequently used International Classification of Medical Procedures codes, and their values in Hungarian Forints [24–26] were used to define the costs of schizophrenia therapies.

To model adverse events as dyskinesia, orthostatic hypotension and sedation and somnolence, the cost of a psychiatrist visit was considered; for clinically significant weight gain, cost of one GP visit was considered. In the case of pseudo-Parkinsonism and akathisia, besides psychiatrist visit, the subsidised drug therapies were also considered, with only the minimal occurring costs were taken into account. For drugs used to treat akathisia, the sum of reimbursed costs was considered as the only factor, which is of concern by NEAK. Cost inputs regarding adverse events are presented in Table 3.

Experts confirmed that the frequency of visits published in the EuroSC database are in accordance with the Hungarian practice on the whole. All costs were converted using the medium Euro (EUR) /Hungarian Forint (HUF) exchange rate of the Hungarian National Bank (2018.04.16.), with the exchange rate of 310.25 HUF per 1 EUR [28].

(b) Utilities

Utilities assigned to the Mohr–Lenert health states were derived from utility values published by Lenert et al. [13]. Utility decrements were assigned to adverse events based on the study of Mohr et al. [12].

(c) Other inputs

The clinical trial showed no association between severity of the disease and mortality, hence we used the same risk ratios reported by Bitter et al. [2] to adjust the mortality of the average population, derived on age-, and gender-specific data from the Hungarian Statistical Office [29,30]. Different mortality rates were tested in the sensitivity analysis. As the time horizon of the analysis exceeds 1 year, the discount rate of 3.7% per year was used for both the costs and health gains, in accordance with the current Hungarian health economic guideline [19]. The latest available GDP per capita figure for Hungary was 11,588 EUR (3609,154 HUF). According to the current health economic guideline [19], the threefold of this is the current cost-effectiveness acceptability threshold in Hungary, which is calculated to be 34,764 EUR (10,827,462 HUF).

(d) Sensitivity analysis

Deterministic sensitivity analyses were conducted on all input parameters, applying a 10% increase and decrease to their values, in accordance with the base-case recommendations of the current Hungarian health economics guideline [19]. Input parameters were also tested using a probabilistic sensitivity analysis (PSA), while scenario analyses were also conducted. In the PSA, Beta distributions were used for transition probabilities, and gamma distributions were used for cost data, with standard deviations in all cases set to be 10%.

Results

Base-case results

The use of cariprazine resulted in 1.45 QALYs and 3340 EUR (1036,278 HUF) total cost per patient, while the use of risperidone resulted in 1.40 QALYs and 1896 EUR (588,216 HUF) total cost per patient over 2 years. The model estimated an additional 0.05 QALY gain with cariprazine compared to risperidone, and an additional

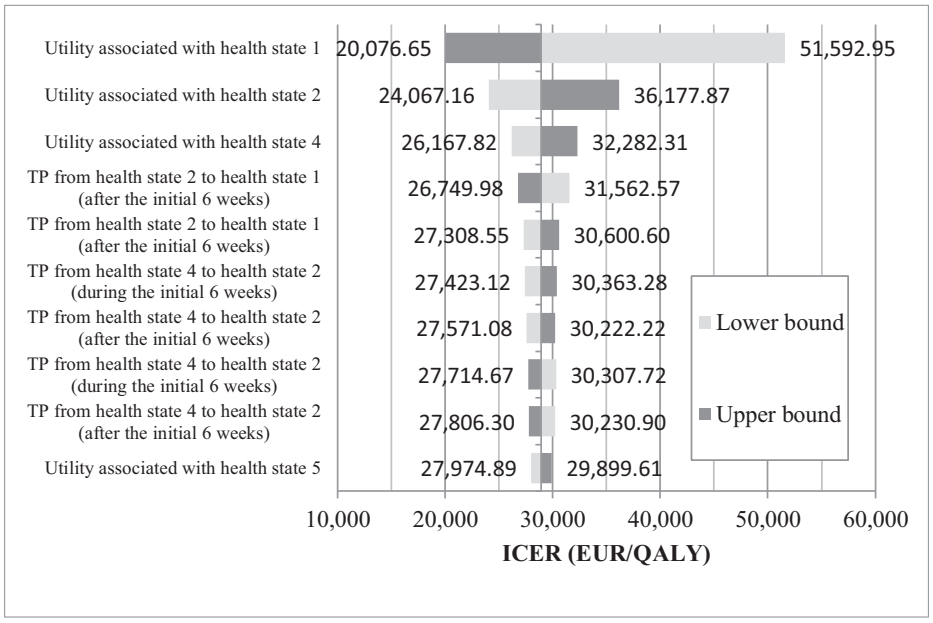

Fig. 1. Tornado diagram.
EUR = Euros; ICER = Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life Year; TP = Transition Probability.

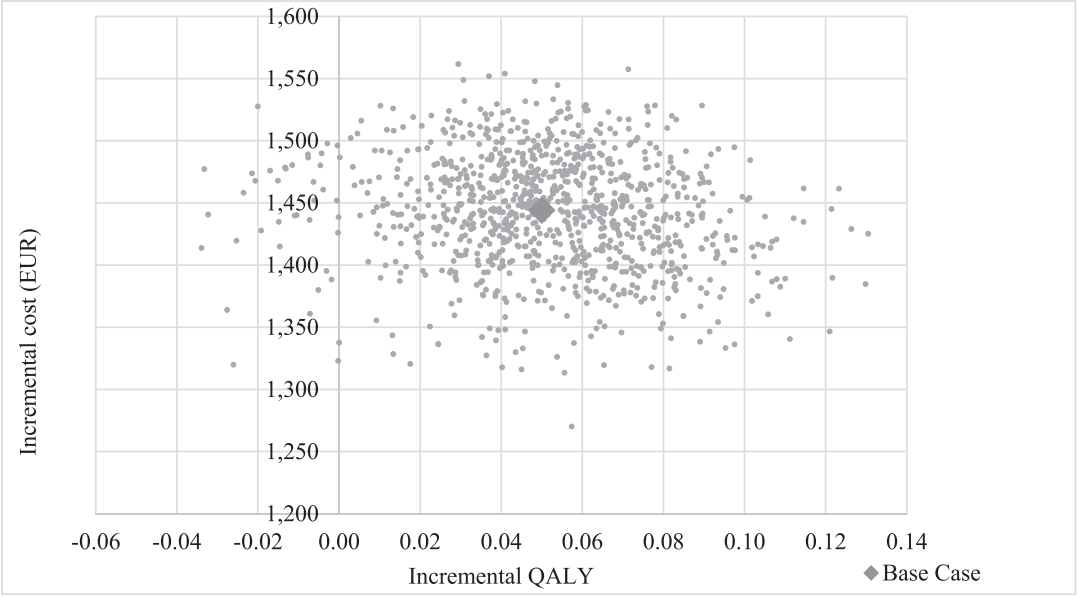

Fig. 2. Results of the Probabilistic Sensitivity Analysis after 1000 runs (scatter plot).
EUR = Euros; QALY = Quality-Adjusted Life Year.

Table 4
Results of the base-case cost-effectiveness calculations.

Item	Quality-adjusted life years over 2 years per patient (standard error based on 1000 PSA runs)	Costs over two years per patient (standard error based on 1000 PSA runs)
Cariprazine arm	1.45 QALY (0.00)	3340 EUR (5.30)
Risperidone arm	1.40 QALY (0.00)	1896 EUR (5.75)
Difference	0.05 QALY (0.00)	1444 EUR (1.44)
Incremental cost-effectiveness ratio		28,897 EUR/QALY (5539.51)

EUR = Euros; PSA = Probabilistic Sensitivity Analysis; QALY = Quality-Adjusted Life Year.

Table 5
Results of the scenario analysis.

Scenarios		ICER (EUR/QALY)	Δ Costs	Δ Effects
1.	Time horizon 10 years (522 weeks)	22,119	2227	0.10
2.	Time horizon 5 years (258 weeks)	23,032	2068	0.09
3.	Time horizon 4 years (210 weeks)	23,737	1964	0.08
4.	Time horizon 3 years (162 weeks)	25,063	1799	0.07
5.	Time horizon 1 year (54 weeks)	37,559	955	0.03
6.	Without therapy switch	31,173	2119	0.07
7.	Comparator: olanzapine	29,117	1404	0.05
8.	With mortality of the average population as a basis	28,881	1447	0.05

EUR = Euros; ICER = Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life Year
Time horizons expressed in years were selected to fit the model cycles (six initial 1-week cycles, followed by 12-week cycles).

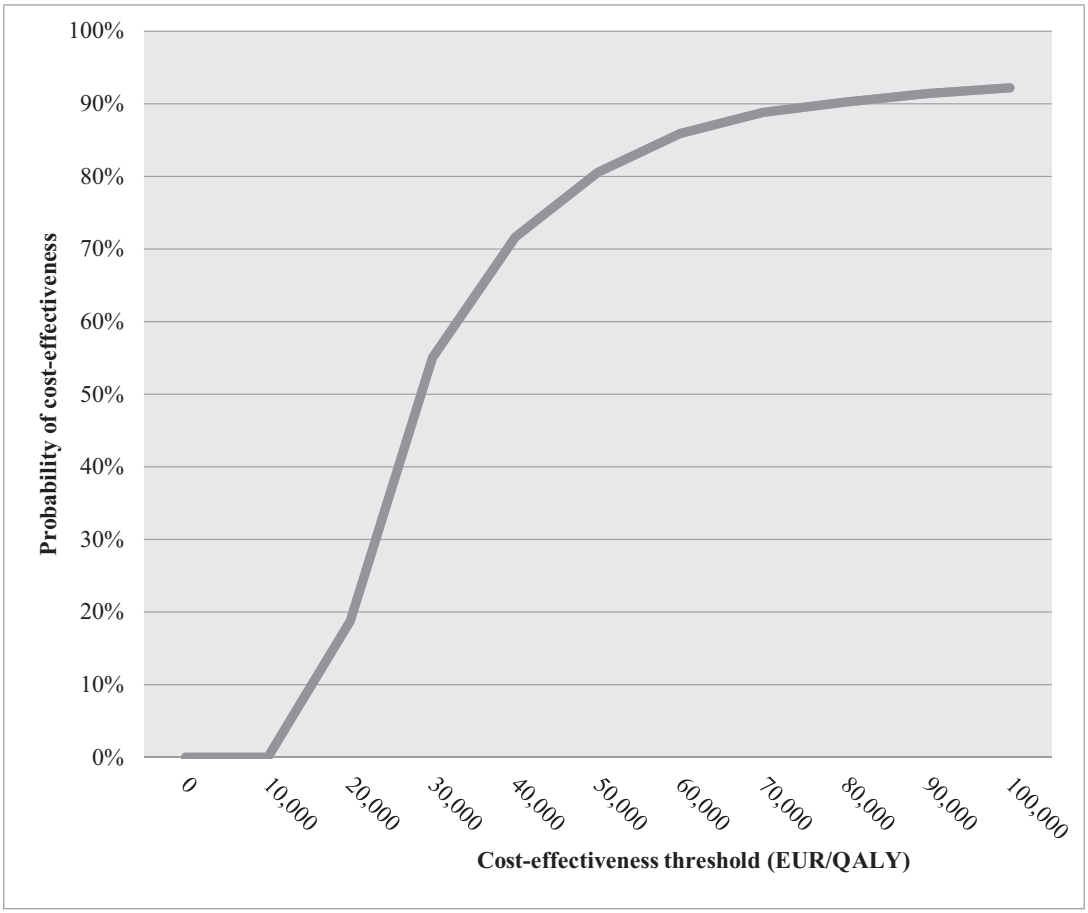

Fig. 3. Results of the Probabilistic Sensitivity Analysis (Cost-Effectiveness Acceptability Curve).
EUR = Euros; QALY = Quality-Adjusted Life Year.

cost of 1444 EUR (448,062 HUF) per patient. The results showed that this difference was lower than the difference in drug prices, due to an estimated lower volume of hospitalization costs on the cariprazine arm. The incremental cost-effectiveness ratio (ICER) of cariprazine compared to risperidone over a 2-year time horizon was resulted in 28,897 EUR/QALY (8965,178 HUF/QALY). Results of the base-case cost-effectiveness calculations are shown in Table 4.

Results of the deterministic sensitivity analysis and scenario analysis

On Fig. 1, the tornado diagram shows that for the majority of cases, the ICER stayed below the current Hungarian cost-effectiveness acceptability threshold. The two exceptions were when changes were applied to the utilities associated with Mohr–Lenert health states 1 and 2.

Results of the scenario analysis are shown in Table 5. The scenario analysis showed that the extended time horizon of the analysis resulted in cost effectiveness values below the current willingness to pay threshold as well. An inverse reaction was observed, with the longer time horizons resulting in lower ICER values. For 10, 5, 4 and 3 years the ICER was 22,119 EUR/QALY, 23,032 EUR/QALY, 23,737 EUR/QALY, and 25,063 EUR/QALY, respectively. Only the scenario with 1-year time horizon resulted in an ICER that was above the willingness to pay threshold (37,559 EUR/QALY).

Using the non-disease specific mortality of the average population also resulted in an ICER below the cost-effectiveness threshold (28,881 EUR/QALY), as well as scenarios without the adaptation of therapy switch and using olanzapine as a comparator (31,173 EUR/QALY; 29,117 EUR/QALY, respectively).

Results of the probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis (Fig. 2 and 3) show that there is more than 70% probability that cariprazine is cost effective, using the Hungarian willingness-to-pay threshold.

Conclusions

This is the first study to assess the cost effectiveness of cariprazine in the treatment of patients with negative symptoms of schizophrenia. According to the willingness to pay threshold in Hungary, cariprazine was compared to the widely used risperidone and olanzapine at acceptable costs. The sensitivity and scenario analyses confirmed the robustness of the analysis but also drew attention on interesting remarks and limitations.

The most important limitations of this study include that while the extremely short (one-year) time horizon and the ignorance of therapy switch are not very likely scenarios, they show the importance of taking long-term treatment effects and other uncertainties into consideration properly. As no evidence from the scientific literature was available describing switching related to Mohr–Lenert health states, the switching feature of the models is based on expert assumptions and on earlier publications [23]. The transition probability matrices derived from the RGH-188-005 clinical trial lacked transition data between numerous health states. Where clinical trial data was unavailable, Bayesian methods were used to gain missing parameters; the method is described in detail by Vokó et al. [20]. As another limitation, adverse events were assumed not to be dependent on health state, which is a conservative assumption as more patients tend to be in better health states on the cariprazine arm, therefore this assumption is likely to overestimate the occurrence of adverse events in the cariprazine arm.

While the current settings and assumptions reflect the Hungarian environment, the methodology used to arrive at these results can be important to other jurisdictions, after considering the transferability of input values [31]. As the observed mechanisms depicted by the model are overwhelmingly generalizable the likelihood of cariprazine being cost-effective in other countries is considerable. Though any cost data are mostly relevant in the specific local setting, the effects on quality of life are likely to be directly transferable. In case of costs, there might be large variations by countries as differences between drug costs and service charges vary substantially (e.g. between Eastern and Western European countries). It is speculated that in countries that have relatively low cost levels for health provisions (e.g. hospital and ambulatory care), the results will show similar patterns to Hungary. While in countries with relatively high level of provision costs, more gains are expected due to avoided institutionalization. These patterns were confirmed by the cost-utility analyses conducted in other countries, including Sweden, Finland, Denmark [32] and Slovakia [33].

The analysis as a whole reflects the Hungarian environment with its local data and assumptions. Future research with little efforts on the collection of local data is encouraged to be dedicated to explore cost-effectiveness in other countries and patient groups.

Funding

Financial support for this study was provided in part by Gedeon Richter Plc., Hungary. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. The following author(s) is/are employed by the sponsor: Árpád Götze, Kristóf Kóczián, Margit Horváth, Izabella Deák, Bernadett Tóth.

Competing interests

Financial support was provided by Gedeon Richter Plc., Budapest, Hungary. Árpád Götze, Kristóf Kóczián, Margit Horváth, Izabella Deák and Bernadett Tóth are employed by Gedeon Richter Plc., Budapest, Hungary, while Bertalan Németh, Rita Bendes, Balázs Nagy and Zoltán Kaló are employees of Syreon Research Institute, which was a contracted research partner of Gedeon Richter Plc. in this project.

Ethical approval

Not required.

Appendix

Table 6–9

Table 6
Weekly transition probabilities between Mohr–Lenert health states used in the cariprazine arm of the model for the first 6 weeks of treatment based on the cariprazine arm of the RGH-188-005 clinical trial and three expert interviews.

FROM [ROW] / TO [COL]	1	2	3	4	5	6	7	8
1	95.55%	1.40%	1.23%	0.51%	0.39%	0.34%	0.36%	0.22%
2	6.05%	86.77%	0.12%	5.23%	1.74%	0.03%	0.03%	0.03%
3	1.98%	59.77%	21.44%	8.02%	3.08%	1.92%	2.69%	1.12%
4	0.01%	19.86%	0.28%	75.28%	0.55%	3.99%	0.01%	0.01%
5	0.04%	22.52%	0.11%	0.10%	70.55%	6.48%	0.13%	0.06%
6	0.01%	3.51%	0.02%	11.97%	10.55%	73.92%	0.02%	0.01%
7	1.58%	2.45%	4.83%	3.50%	23.12%	13.31%	45.80%	5.41%
8	2.37%	2.48%	4.47%	7.18%	9.60%	20.59%	7.42%	45.90%

Source: Németh et al. [17].

Table 7
Weekly transition probabilities between Mohr–Lenert health states used in the risperidone arm of the model for the first 6 weeks of treatment based on the risperidone arm of the RGH-188-005 clinical trial and three expert interviews.

FROM [ROW] / TO [COL]	1	2	3	4	5	6	7	8
1	94.11%	1.80%	1.60%	0.68%	0.55%	0.47%	0.51%	0.28%
2	3.35%	80.72%	0.12%	9.13%	5.78%	0.85%	0.03%	0.03%
3	1.33%	6.60%	80.97%	5.23%	2.09%	1.31%	1.76%	0.71%
4	0.01%	22.07%	0.57%	74.24%	0.85%	2.23%	0.01%	0.01%
5	0.03%	15.83%	0.09%	3.61%	74.71%	5.56%	0.11%	0.05%
6	0.01%	2.88%	0.01%	8.90%	12.08%	76.09%	0.02%	0.01%
7	1.49%	2.37%	4.98%	3.46%	23.01%	13.25%	45.98%	5.46%
8	2.22%	2.51%	4.51%	7.04%	9.62%	20.56%	7.41%	46.15%

Source: Németh et al. [17].

Table 8
12-week transition probabilities between Mohr–Lenert health states used in the cariprazine arm of the model for the latter stages of treatment based on the cariprazine arm of the RGH-188-005 clinical trial and three expert interviews.

FROM [ROW] / TO [COL]	1	2	3	4	5	6	7	8
1	93.26%	5.80%	0.25%	0.22%	0.17%	0.20%	0.06%	0.05%
2	18.28%	75.27%	0.70%	1.37%	3.68%	0.68%	0.02%	0.01%
3	35.16%	8.60%	45.67%	4.49%	2.60%	1.64%	1.07%	0.75%
4	3.67%	42.00%	0.13%	50.36%	2.47%	1.26%	0.07%	0.05%
5	6.67%	39.36%	2.33%	0.27%	44.34%	6.77%	0.16%	0.11%
6	1.53%	22.19%	1.56%	11.90%	22.31%	40.35%	0.09%	0.07%
7	2.31%	4.18%	6.49%	9.33%	27.75%	16.22%	27.32%	6.41%
8	1.51%	3.17%	5.22%	10.57%	18.79%	28.66%	13.70%	18.39%

Source: Németh et al. [17].

Table 9
12-week transition probabilities between Mohr–Lenert health states used in the risperidone arm of the model for the latter stages of treatment based on the risperidone arm of the RGH-188-005 clinical trial and three expert interviews.

FROM [ROW] / TO [COL]	1	2	3	4	5	6	7	8
1	75.85%	23.05%	0.28%	0.26%	0.20%	0.23%	0.07%	0.06%
2	13.94%	80.55%	0.04%	0.75%	4.31%	0.38%	0.02%	0.01%
3	2.48%	62.93%	18.56%	6.93%	3.84%	2.45%	1.59%	1.23%
4	1.09%	21.71%	0.11%	74.80%	0.08%	2.11%	0.06%	0.04%
5	6.66%	39.61%	0.09%	0.16%	47.93%	5.39%	0.10%	0.07%
6	0.06%	26.85%	0.11%	6.81%	15.24%	50.75%	0.11%	0.08%
7	2.29%	4.12%	6.58%	9.33%	27.57%	16.24%	27.59%	6.30%
8	1.55%	3.08%	5.40%	10.68%	18.70%	28.82%	13.51%	18.26%

Source: Németh et al. [17].

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