Original paper

Cost-utility analysis of Ruconest® (conestat alfa) compared to Berinert® P (human C1 esterase inhibitor) in the treatment of acute, life-threatening angioedema attacks in patients with hereditary angioedema

Paweł Kawalec[1,2], Przemysław Holko[2,3], Anna Paszulewicz[2,4]

[1]Drug Management Department, Institute of Public Health, Faculty of Health Sciences, Jagiellonian University, Krakow, Poland
 Head: Prof. Andrzej Pilc
[2]Centrum HTA, Krakow, Poland
 Head: Dr. Paweł Kawalec
[3]Department of General Biochemistry, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland
 Head: Prof. Andrzej Klein
[4]Laboratory of Cell Biophysics, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland
 Head: Dr. Joanna Bereta

Abstract

Introduction: Administration of human C1 esterase inhibitor (Berinert® P) from target import is the most widespread treatment strategy for patients with hereditary angioedema (HAE). However, a therapeutic health program including Ruconest® (conestat alfa) could shorten a patient's expectancy for a life-saving treatment.

Aim: To evaluate the cost-utility of Ruconest® (conestat alfa) financed from public funds within the newly introduced therapeutic health program compared with Berinert® P (human C1 esterase inhibitor) in the treatment of acute angioedema attacks in adults with HAE.

Material and methods: The cost-utility analysis from the Polish healthcare payer's perspective was performed for 1 year (2012). The costs and health outcomes were simulated for three pairs of eligible HAE patient groups (active treatment and corresponding placebo). The incremental costs of each intervention compared with placebo were listed together (direct or indirect comparisons between options were impossible due to limited clinical data available).

Results: The incremental cost-utility ratios (ICURs) for the evaluated interventions compared with placebo were as follows: EUR 15,226 per QALY (Ruconest®) and EUR 27,786 per QALY (Berinert® P). The probability of cost-utility (ICUR < EUR 24,279 per QALY) assessed for Ruconest® administered in the case of acute angioedema attack was 61% and 41% for Berinert® P.

Conclusions: The administration of Ruconest® in acute life-threatening angioedema attacks is economically justified from the Polish healthcare payer's perspective, results in lower costs and is characterized by higher cost-utility probability compared with Berinert® P.

Key words: acute angioedema attacks, conestat alfa, cost-utility analysis, hereditary angioedema, human C1 esterase inhibitor.

Introduction

Hereditary angioedema (HAE) caused by C1-esterase inhibitor deficiency is an autosomal-dominant disease, although 25% of cases can occur as a result of de novo mutations [1]. Hereditary angioedema is characterized by recurrent attacks of intense, massive, localized subcutaneous edema (involving the extremities, genitalia, face or trunk) or submucosal edema (of the upper airway or bowels) [2, 3]. Most HAE patients have either a quantitative (type I) or functional (type II) defect in the C1 inhibitor (C1-INH). Type III, which is characterized by normal quantitative and functional

C1-INH levels and estrogen dependence, occurs more frequently in females [4]. Studies based on national HAE registries show a minimal prevalence ranging from 1.09 to 1.51 in 100,000 inhabitants [5-7]. Estimates indicate that approximately 1 in 50,000 people in the general population has HAE [8]. The number of Polish patients with hereditary angioedema (HAE) was assessed at 242 cases (including children and adults) on the basis of the registry of the Polish Aid Association for Patients with Hereditary Angioedema [4]. In addition, some sources indicate that the Polish HAE population could reach even 500-700 patients [4]. The problem is that there are a lot of patients who did not suffer an angioedema attack strong enough for HAE diagnosis or the disease symptoms were wrongly recognized.

Over the last decade, the management of HAE has been dramatically changing. Numerous C1-INH replacement options are used. Human C1-INH is a plasma serine protease inhibitor that inhibits proteases in the coagulation/fibrinolytic system, the complement system, and the kinin system [9].

Conestat alfa (Ruconest®), recombinant human complement component 1 (C1) esterase inhibitor (rhC1INH), is an analogue of human C1-INH and is obtained from the milk of rabbits expressing the gene encoding for human C1-INH. The amino acid sequence of conestat alfa is identical to that of endogenous C1-INH. Inhibition kinetics was found to be comparable with those observed for plasma-derived human C1-INH [10].

In the actual clinical practice in Poland [11-13], the administration of the human C1 esterase inhibitor (Berinert® P) is the most widespread strategy. It can be used in the framework of target import procedure as well as fresh frozen plasma (FFP) in single cases but it is a very inconvenient and time-consuming procedure (those medical products are reimbursed on the basis of individual patient's application and the number of vials is limited). In terms of the current situation, an introduction of the new therapeutic health program including reimbursed C1 esterase inhibitor (Ruconest®) could shorten a patient's expectancy for a life-saving treatment. The inclusion criteria of the mentioned therapeutic health program should include acute angioedema attacks in adults with diagnosed C1 esterase inhibitor deficiency (types I and II) while patients ought to be excluded in the case of known or suspected allergy to rabbits or hypersensitivity to the active substance (conestat alfa) or to any of the excipients.

In this paper we evaluate the cost-utility of Ruconest® (conestat alfa) compared with Berinert® P (the human C1 esterase inhibitor) in the treatment of acute angioedema attacks in adults with HAE due to C1 esterase inhibitor deficiency in a Polish setting.

Material and methods

Cost-utility analysis

The disease model was designed to calculate the costs and effects associated with the treatment of acute angioedema attacks in adults with HAE. The effects were expressed in non-monetary units, such as life years gained (LYG) or quality adjusted life years gained (QALYG). The final results were expressed as the incremental cost-utility ratio (ICUR), which is defined as the ratio of the difference in costs to the difference in effects between the active treatment and corresponding placebo: ICUR = $(C_a - C_b)/(E_a - E_b)$, where C_i is the cost and E_i is the effect of an intervention (a or b) [14]. The cost-utility of the therapy was assumed when the ICUR was lower than EUR 24,279 (PLN 99,543) per QALY, which is set as threshold acceptability in Poland (tripled GDP per capita) [15].

Population

The population consisted of HAE patients with C1-esterase inhibitor deficiency with the risk of an acute angioedema attack. The model simulated two cohorts of eligible patients treated with one of the following: conestat alfa (50 U/kg) or human C1-INH (20 U/kg) and two corresponding cohorts of HAE patients without any active treatment (equivalent to placebo). In all of the above cohorts, patient characteristics (in each simulation) were the same (the course of angioedema attack treated with compared drugs was simulated in identical populations). Patients were observed between and during angioedema attacks.

Discrete event simulation model

Discrete event simulation (DES) is one way of observing the time-dependent (or dynamic) behavior of a system [16]. It was proposed as a computational tool for cost effectiveness analyses and the key principles of the method were reiterated: entities, events and time [17]. Entities are the items that evolve through the simulation – and in the clinical models these are usually patients who are assigned attributes (e.g. age, sex, duration of the disease) with a specific value (distribution) each. These values are defined at the start of the simulation and may be updated as required: age increases, disease severity levels rise and fall, etc. Other model specifications such as time horizon and discount rate are encoded in variables and they may change during the simulation. An event is defined as anything that can happen during the simulation. This can include occurrence of a period without attacks, acute attack, life-threatening attack and death, etc. The events can change the course of a given patient's experience by influencing that patient's attributes and the occurrence of future events. The rates at which events occur can take on any functional distribution supported by the data. They can be dependent on any attributes or variables and these functions can change over time as appropriate. The third fundamental component of a DES is time itself. An explicit simulation clock keeps track of the passage of time [17, 18].

The brief model scheme using discrete event simulation is presented in Figure 1 and main model parameters are shown in Table 1. Time horizon was set at one year, which
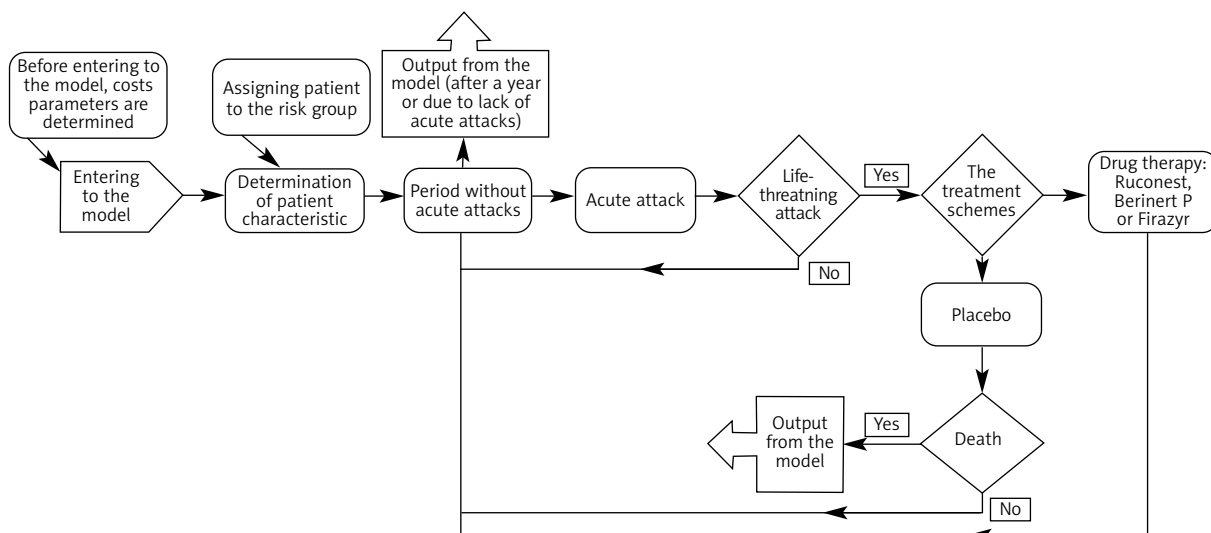
Fig. 1. The scheme of the model using discrete event simulation

Table 1. List of the parameters used as a model input

Model parameters	Value*	Comment
Product price Ruconest®	EUR 1,174.76 (PLN 4,816.52)	The product is not available in Poland
Product price Berinert® P	EUR 932.52 (PLN 4,029.29)	The product is financed by the public payer within the target import procedure – as a life saving drug
Average patient body weight	76.95 kg	
Mode of drug administration – Ruconest®, Berinert® P,	Outpatient procedure: 80% hospitalization < 2 days: 10% hospitalization for > 1 day: 10%	
Cost of inpatient and outpatient care (per acute attack of angioedema)	Ruconest®: EUR 60.24 (PLN 247.0), Berinert® P: EUR 91.51 (PLN 357.20)	
Cost of diagnostics (annually)	Ruconest®: EUR 90.92 (PLN 372.78) Berinert® P: diagnostic tests are carried out in the framework of inpatient and outpatient services related to the administration of drugs in the treatment of acute life-threatening angioedema attack	Min: EUR 68.19 (PLN 279.59) Max: EUR 124.39 (PLN 510.0)
Death risk in placebo cohorts	30%	
Life-threatening acute attacks	5%	
Percentages of patients in the target population divided by risk of an acute attack	High risk: 40.7% Moderate risk: 49.7% Low risk: 5.0% Absence of seizures: 4.6%	
Number of acute attacks per year per patient according to risk groups of an acute attack	High risk: 13.0 Moderate risk: 8.5 Low risk: 3.0 Absence: 0.0	From minimum to maximum: high risk: 12 to 14, moderate risk from 6 to 11, low risk: 1 to 5
The life quality of a patient between angioedema attacks	0.9	Average life quality of patients from the general population
The life quality of a patient at the maximum intensity of attack	0.315	Based on severity of the symptoms
Willingness to pay (WTP)	EUR 24,278.78 (PLN 99,543.00)	Assuming tripled GDP per capita cost-utility threshold [18]

*Assuming that EUR 1 = PLN 4.10

seemed to be a reasonable compromise between the short clinical trials observation time and the median life expectancy horizon. The patient's observation during the period between attacks was performed with 1-day accuracy and during the acute, life-threatening attack was monitored with 1-hour precision. The simulation was performed for all patients from the estimated population and repeated 1,000 times while cost and efficacy parameters were randomized in accordance with their probability distributions. Firstly, the model counted average costs (average total cost and average cost parameters) and health outcomes (quality-adjusted life years) per patient, assuming all parameters were constant (except for patient characteristics) and after that the average annual costs and health effects were summarized considering all model parameters as variable (according to assumed probability distributions).

Clinical data

The clinical data input is based on the systematic search of medical databases [19] performed by two analysts working independently and conducted according to the Evidence Based Medicine standards [20], Cochrane Collaboration [21] and Polish Health Technology Assessment Agency (*Agencja Oceny Technologii Medycznych;* AOTM) Guidelines [22] that yielded two placebo-controlled studies for conestat alfa (Ruconest®) [23, 24] and two for human C1-INH (Berinert® P) [25-31]. No head-to-head trials comparing the interventions were identified and due to significant heterogeneity between trials (differences in inclusion criteria and assessing endpoints) a reliable indirect comparison through a common comparator between trials was also impossible [32]. Consequently, the analysis consisted of the collated results obtained for direct comparisons with placebo for all interventions of interest. The probability of acute life-threatening attack of angioedema was additionally assessed on the authority of clinical experts from the Department of Clinical and Environmental Allergology, Jagiellonian University Medical College. The treatment efficacy was measured as: time to first improvement of symptoms and the time to almost complete symptom relief and the probability of the intervention success. Due to the negative impact of acute angioedema attacks on the life quality of patients [33, 34], the decrease in life quality between and during angioedema attacks was simulated. It was assumed that life quality could be assessed from 0 (*death*) to 1 (*perfect health*). The Cost Effectiveness Analysis Registry Database was searched and two publications including information about life quality of patients with hereditary angioedema (SF-36 scale [35], SF-12 scale [36]) were found. However, no studies were found describing life quality during angioedema attacks, therefore decrease in life quality was simulated on the basis of measurement in VAS (Visual Analog Scale, which was used in clinical trials to measure symptom intensity of angioedema attacks). Symptom intensity according to VAS ranges from 0 mm (*no heredi-*

tary angioedema), which meant no decrease in life quality, to 100 mm (*extremely disabling*) [23, 24] which meant maximum worsening of life quality. Due to lack of appropriate data, the life quality between angioedema attacks was set at 0.9 (average life quality in the general population) [37]. Patients belonging to the cohorts that were not actively treated could die from an acute life-threatening angioedema attack (death risk was estimated at 30% [38, 39]) and according to the clinical trial results, mortality was not considered among patients treated with active drugs (Ruconest®, Berinert® P). Due to a relatively short time horizon, mortality from causes other than acute attack of angioedema was omitted. It should be also stressed that lack of active treatment (equivalent to placebo in clinical trials) is not a real (used in clinical practice) comparator for assessed treatment options (conestat alfa, human C1-INH). However, due to the heterogeneity of the clinical trials assessing the efficacy and safety profile of the compared medical products, a reliable direct comparison of costs and health outcomes was not possible.

Costs

Medical resources used and cost categories were indentified according to the data from the Department of Clinical and Environmental Allergology, Jagiellonian University Medical College. The cost was assessed in PLN and subsequently calculated in EUR (based on the average EUR/PLN exchange rate in 2011). The analysis included direct healthcare costs from the perspective of healthcare payer according to Polish AOTM guidelines [22]. Payments out of the public healthcare budget as well as patients' co-payments were included. It was assumed that Ruconest® (conestat alfa) would be financed from public funds within a newly introduced therapeutic health program. The direct medical costs were assessed on the basis of the literature review and information provided by the National Health Fund outlined in the regulations [40-42] and included: cost of human C1-INH (at present, human C1-INH is financed by the public payer within a target import procedure – as a lifesaving drug – and its cost amounts to EUR 0.78 for each patient), cost of conestat alfa, cost of fresh frozen plasma (currently financed by the public payer), cost of inpatient and outpatient care during the administration of compared treatment options (currently financed by the public payer), cost of diagnostic procedures (currently financed by the public payer). There were no direct non-medical costs included in the analysis (e.g. transport costs, infrastructure costs) due to lack of data. No influence of HAE on other members of society than patients or on productivity was found. Social perspective was not considered. Additional or indirect lost productivity costs were ignored.

The price of conestat alfa used within the new introduced therapeutic health program was based on information from Swedish Orphan Biovitrum Sp. z o.o. Branch in Poland, Value Added Tax and wholesale margin [43, 44].

The wholesale price of conestat alfa was assessed at EUR 1,174.76 in 2012 (this price was used for simulation). The price of human C1-INH from target import was assessed at EUR 932.52 and both these prices were tested in sensitivity analysis. The consumption of compared treatment options was estimated on the basis of Summaries of Product Characteristics [8, 45] and the results of clinical trials [38, 39]. The average consumption of administered drugs during a single, acute, life-threatening angioedema attack was estimated at 1.83 vials of conestat alfa and 3.58 vials of human C1-INH. In the framework of the therapeutic health program, the Polish National Health Fund covers only cost of used vial of conestat alfa while the rest is utilized and its cost is covered by healthcare providers (hospitals, dispensaries). During target import of human C1-INH, the public payer covers also the cost of the unused part of vial. Consumption of assessed active substances was tested during sensitivity analysis and the following parameters were changed: average body weight (minimum and maximum), percentage of patients involving the second drug administration (according to ranges of 95% confidence interval), average number of used vials of human C1-INH (3-4). Fresh frozen plasma is administered in special cases (lack of conestat alfa and human C1-INH) in actual clinical practice and its cost (without administration cost) amounted to EUR 63.44. Inpatient and outpatient administration costs were estimated on the basis of the questionnaire study and amounted to PLN 348.5 (administration of human C1-INH) and EUR 59.09 (in the case of conestat alfa administration). When the new therapeutic health program is introduced, the cost of diagnostic procedures would be included in the cost of the program itself. It would be an annual lump sum equal to product of the outpatient administration cost and average number of acute life-threatening angioedema attacks. Outpatient administration was assumed as the cheapest option to be used in the diagnostic procedures in acute life-threatening angioedema attacks. In the analysis, total annual cost of diagnostic procedures was assessed at EUR 85.37 per patient. Before starting up the treatment with conestat alfa, examination against allergy for rabbits should be conducted, however, their cost would be covered by the producer.

Results

In the base case analysis with a one year's perspective, patients with HAE suffering from life-threatening angioedema attacks gained on average 0.0261 quality adjusted life years (QALY) when treated with Ruconest® (conestat alfa) and 0.0262 QALY when treated with Berinert® P compared with placebo (Table 2). One can conclude that the difference in health outcomes between interventions were negligible. The incremental costs of the therapy of a single acute angioedema attack with conestat alfa amounted to app. EUR 419, app. EUR 755 per patient for human C1-INH treatment in comparison with placebo, thus indicating that conestat alfa is the cheapest option (Table 2). The median incremental cost-utility ratios for assessed interventions compared with placebo were as follows: EUR 15,226 per QALY (conestat alfa) and EUR 27,786 per QALY (human C1 esterase inhibitor) – Table 2. The results proved that Ruconest® (conestat alfa) was cost-effective in comparison to no active treatment (placebo) in the therapy of acute life-threatening angioedema attacks in adults with HAE due to C1 esterase inhibitor deficiency – median of incremental cost-utility ratios was lower than the assumed threshold, EUR 24,279 per QALY. On the basis of probabilistic analysis (which includes 1,000 simulations of the disease with the variability of the model parameters presented in Table 1 within assumed boundary values and their distribution), the likelihood of cost utility (ICUR value below EUR 24,279 threshold) was estimated at 41% for Berinert® P and 64% for Ruconest®. The acceptability curves for each drug technology (Figure 2) are depicting the percent of the simulations where each of the treatments achieved the cost-utility level depending on the assumed threshold meaning willingness-to-pay from the healthcare payer's perspective for an additional quality adjusted life year. It has been shown that the use of Ruconest® financed within the newly introduced therapeutic health program in place of the placebo associated with potentially lower overall cost compared with Berinert® P.

Discussion

Results of the cost-utility analysis proved that the administration of Ruconest® (conestat alfa) within the therapeutic

Table 2. Results of the cost-utility analysis

Parameter	Ruconest®	Berinert® P
Quality-adjusted life years (QALY) in comparison to placebo (median)*	0.0261 QALY	0.0262 QALY
Total incremental costs in comparison to placebo (median)**	EUR 419.27[#] (PLN 1,719)	EUR 754.63[#] (PLN 3,094)
Incremental Cost-Utility Ratio (ICUR) in comparison to placebo (median)	EUR 15,225.61[#] per QALY (PLN 62,425 per QALY)	EUR 27,786.34[#] per QALY (PLN 113,924.00 per QALY)
Percentage of simulations where treatment option was cost-effective in comparison to placebo	64%	41%

*p = 0.346, medians were not significantly different; **p < 0.0001, medians were significantly different; [#]assuming that EUR 1 = PLN 4.10

health program would create a profitable treatment option from a payer's perspective (National Health Fund and patient). The administration of Ruconest® (conestat alfa) was associated with higher probability of cost-utility. Additionally, the positive decision about financing of Ruconest® (conestat alfa) within the therapeutic health program in the assessed medical indication has other advantages. Introduction of the therapeutic health program would assure permanent access (in the case of a direct life threat caused by an acute angioedema attack) to effective treatment options for patients with HAE. According to Polish and international guidelines, Ruconest® (conestat alfa) should be administered whenever there is a significant therapeutic indication [11-13, 26-46].

Surely, the absence of direct or indirect comparison between the treatment options is a limitation of the analysis, but it was impossible to perform such collation due to the lack of appropriate clinical data (no head-to-head trials and significant heterogeneity between placebo controlled trials). It should be stressed that lack of the active treatment (equivalent to placebo in clinical trials) is not a real (used in clinical practice) comparator for assessed treatment options (conestat alfa, human C1-INH).

It might appear that the one-year time horizon was assumed arbitrarily. Though, the choice is justified because the administration of Ruconest® (conestat alfa) and Berinert® P (human C1-INH) prevented death to the same extent, therefore considering costs and health outcomes (quality-adjusted life years) in a time horizon longer than one year could solely multiply differences observed in one year. The choice of 1-year horizon decreased incremental changes between Ruconest® and the comparator which was a conservative assumption when taking into account higher clinical efficacy of Ruconest®.

There was no possibility to assess precisely costs of diagnostic procedures settled within the potentially introduced therapeutic health program. Estimation of these costs was based on the assumption that they would be introduced as an annual lump sum equal to the product of the average number of acute, life-threatening attacks and in-hospital administration cost. Still, testing of these assumptions within sensitivity analysis (cost summary) did not significantly influence the assumed costs.

Moreover, the life quality during an angioedema attack was assessed as a result of modeling (based on severity of the symptoms) and the life quality in the period between angioedema attacks was assumed arbitrarily at a level of 0.9 (due to lack of relevant data) – so the quality of life in the health states included are still a rough estimate of the reality.

The sensitivity analysis proved assumptions from basic analysis and showed that the use of Ruconest® within the newly introduced therapeutic health program is associated with a potentially lower cost from the perspective of the payer than the use of Berinert® P.
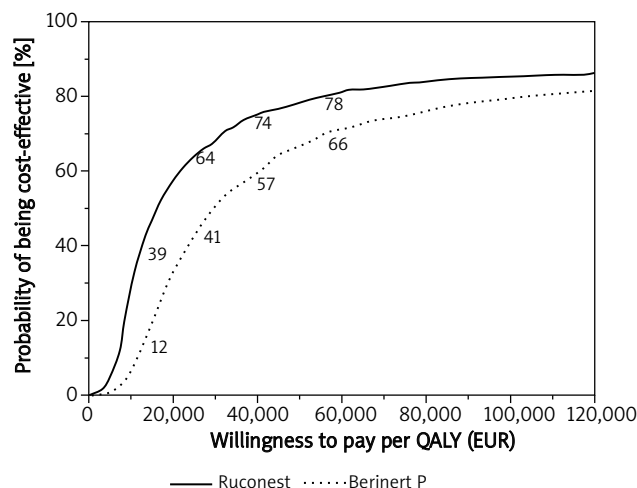

Fig. 2. Cost-effectiveness acceptability curve indicating the proportion of simulations, where each treatment (Ruconest® or Berinert® P) is cost-effective compared to placebo at various willingness to pay thresholds

Acknowledgments

References

1. Roche O, Blanch A, Caballero T, et al. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. Ann Allergy 2005; 94: 498-503.
2. Zuraw BL. Hereditary angioedema. N Engl J Med 2008; 359: 1027-36.
3. Frank MM. Hereditary angioedema: the clinical syndrome and its management in the United States. Immunol Allergy Clin North Am 2006; 26: 653-68.
4. Official website of Polish Aid Association for Patients with Hereditary Angioedema, http://www.hae.org.pl/ (last access: 1.09.2012).
5. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. Br J Dermatol 2009; 161: 1153-8.
6. Roche O, Blanch A, Caballero T, et al. Hereditary angioedema due to C1 inhibitor deficiency: patent registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol 2005; 94: 498-503.
7. Stray-Pedersen A, Abrahamsen TG, Froland SS. Primary immunodeficiency diseases in Norway. J Clin Immunol 2000; 20: 477-85.
8. Bowen T, Cicardi M, Bork K, et al. Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. Ann Allergy Asthma Immunol 2008; 100 (Suppl 2): 30-40.
9. Davis AE, Lu F, Mejia P. C1 inhibitor, a multi-functional serine protease inhibitor. Thromb Haemost 2010; 104: 886-93.
10. Summary of Product Characteristics – Ruconest? (last updating: 1.09.2012).

11. Obtułowicz K. Hereditary angioedema due to C1 inhibitor deficiency. Diagnostic issues and current treatment. Alergol Immunol 2010; 7: 86-8.

12. Obtułowicz K. Report from international experts' conference for the Hereditary Angioedema. Alergol Immunol 2010; 7: 3-4.

13. Muszyńska A, Fal AM. Hereditary angioedema – treatment. Pol Merkuriusz Lek 2008; 145: 94-6.

14. Szmurło D, Schubert A, Kostrzewska K, et al. Economic analysis of the implementation of guidelines for type 2 diabetes control developed by Diabetes Poland. Pol Arch Med Wewn 2011; 121: 345-51.

15. Official website of Main Statistical Office, information about actual 2012 GDP estimation http://www.stat.gov.pl/gus/5840_1338_PLK_ HTML.htm (last access: 1.09.2012).

16. Jacobson S, Hall S, Swisher J. Discrete event simulation of health care systems. In: Delay management in healthcare systems. Hall R (ed.). Springer in Health Care Management 2006.

17. Caro JJ. Pharmacoeconomic analyses using discrete event simulation. Pharmacoeconomics 2005; 23: 323-32.

18. Le Lay A, Despiegel N, François C, Duru G. Can discrete event imulation be of use in modelling major depression? Cost Eff Resour Alloc 2006; 4: 19.

19. Lesniak W, Bala M, Jaeschke R, et al. Effect of megestrol acetale in patients with cancer anorexia-cachexia syndrome – a systematic review and meta-analysis. Pol Arch Med Wew 2008; 118: 636-44.

20. Gajewski P, Jaeschke R, Brożek J. Basis of EBM, medicine based on scientific data for physicians and medical students. Medycyna Praktyczna 2008.

21. Cochrane Collaboration, Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. March 2011 (http://www.cochrane.org/resources/handbook/) – last access: 1.09.2012.

22. Guidelines for conducting Health Technology Assessment HTA. Version 2.1. AHTAPol March 2009 (last access: 1.09.2012).

23. Results of C1 1205-01 trial provided by Swedish Orphan Biovitrum Sp. z o.o., Division in Poland (data on file); RhC1INH (Ruconest®) vs. placebo.

24. Results of C1 1304-01 trial provided by Swedish Orphan Biovitrum Sp. z o.o., Division in Poland (data on file); RhC1INH (Ruconest®) vs. placebo.

25. Caballero T, et al. European consensus for gynecologycal and obstetric management of women with hereditary angioedema due to C1-Inhibitor deficiency (HAE): PREHAEAT. J Allergy Clin Immunol 2007; S12.

26. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management. Allergy Asthma Clin Immunol 2010; 6: 24.

27. Kunschak M, Engl W, Maritsch F, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. Transfusion 1998; 38: 540-9.

28. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. N Engl J Med 1996; 334: 1630-4.

29. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol 2009; 124: 801-8.

30. Bernstein JA, Ritchie B, Levy RJ, et al. Hereditary angioedema: validation of the end point time to onset of relief by correlation with symptom intensity. Allergy Asthma Proc 2011; 32: 36-42.

31. Krassilnikova S, Craig ET, Craig TJ. Summary of the international, prospective Angioedema C1-inhibitor trials 1 and 2 (IMPACT1 and 2). Expert Rev Clin Immunol 2010; 6: 327-34.

32. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50: 683-91.

33. Dagen C, Craig TJ. Treatment of hereditary angioedema: items that need to be addressed in practice parameter. Allergy Asthma Clin Immunol 2010; 6: 11.

34. Kreuz W, Martinez-Saguer I, Aygören-Pürsün E, et al. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. Transfusion 2009; 49: 1987-95.

35. Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. Eur J Dermatol 2009; 19: 147-51.

36. Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. Allergy Asthma Proc 2010; 31: 407-14.

37. Golicki D, Niewada M, Jakubczyk M, et al. Self-assessed health status in Poland: EQ-5D findings from the Polish valuation study. Pol Arch Med Wewn 2010; 120: 276-81.

38. Agostoni A, Aygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress. Proceedings of the third C1 Esterase Inhibitor Deficiency Workshop and beyond. J Allergy Clin Immunol 2004; 114: 51-131.

39. Bork K, Ressel N. Sudden upper airway obstruction in patients with hereditary angioedema. Transfus Apher Sci 2003; 29: 235-8.

40. National Health Fund Official Website. Agreement Registry. http://www.nfz.gov.pl/new/index.php?katnr=3&dzialnr=19 (last access: 1.09.2012).

41. National Health Fund. National Health Fund. Ambulatory groups of specialist services catalog – appendix 5a to Regulation no. 81/2011/DZOZ of National Health Fund President from 4th November 2011.

42. National Health Fund, National Health Fund. Groups catalogue – appendix 1 to Regulation no. 11/2012/DZOZ of National Health Fund President from 28th February 2012.

43. Paragraph 2, article 41, clause 1, section VIII of Act from 11th March 2004 for the goods and services tax.

44. Legal act on drug and medical devices reimbursement – 12.5.2011.

45. Summary of Product Characteristics – Berinert® P (last updating: 1.09.2012).

46. Bowen T, Brosz J, Brosz K, et al. Management of hereditary angioedema: 2010 Canadian approach. Allergy Asthma Clin Immunol 2010; 6: 20.