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

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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...
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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 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 – C)/ (E – E), where C is the cost and E 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...
Before entering to the model, costs parameters are determined
Assigning patient to the risk group
Determining of patient characteristic
Period without acute attacks
Acute attack
Life-threatening attack
The treatment schemes
Drug therapy: Ruconest, Berinert P or Firazyr
Placebo
Output from the model

**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 | 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) Min: EUR 68.19 (PLN 279.59) Max: EUR 124.39 (PLN 510.0) |
| 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 |
| 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 assessed in PLN and subsequently calculated in EUR (based on the average EUR/PLN exchange rate in 2011). The analysis included 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 diagnostic procedures (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.

**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 life-saving 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 (cost 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 was 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®.

### Discussion

Results of the cost-utility analysis proved that the administration of Ruconest® (conestat alfa) within the therapeutic health program in place of the placebo associated with potentially lower overall cost compared with Berinert® P.

#### 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 a (PLN 1,719) | EUR 754.63 a (PLN 3,094) |
| Incremental Cost-Utility Ratio (ICUR) in comparison to placebo (median) | EUR 15,226.61 a per QALY (PLN 62,425 per QALY) | EUR 27,786.34 a 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, aassuming 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 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.

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