Recommendation No 10/2021

of 4 February 2021

of the President of the Agency for Health Technology Assessment and Tariff System

on the evaluation of Firazyr (icatibant) for the indication:

symptomatic treatment of acute, life-threatening attacks of hereditary angioedema in adolescents and children 2 years of age and over with C1 esterase inhibitor deficiency

The President of the Agency recommends the reimbursement of the medicinal product Firazyr (icatibant) for the indication: symptomatic treatment of acute, life-threatening attacks of hereditary angioedema in adolescents and children aged 2 years and over with C1 esterase inhibitor deficiency

Explanation for recommendation

Taking into account the position of the Transparency Council, available scientific evidence, clinical guidelines and reimbursement recommendations, the President of the Agency, considers the public financing of the technology named in the application to be justified.

It was considered that an acute attack of hereditary angioedema (HAE) caused by C1 esterase inhibitor deficiency, occurring in the upper respiratory tract, is associated with an immediate threat to the patient's life and the condition itself is classified as a rare disease.

The indication covered by the order is consistent with the registration indication for the medicinal product Firazyr (icatibant); at the same time, the drug is currently on the list of reimbursed drugs and is used in the adult population. No studies were found that would directly compare the technology analysed with selected comparators. The process of drawing conclusions on the medicinal product under evaluation, Firazyr, is based on a single-arm study conducted in a small group of paediatric patients (N=32). At the same time, the evaluation of efficacy for the proposed technology in relation to the comparator was possible only by comparing the results of studies for individual drugs.

The clinical analysis does not allow concluding that there are differences in the efficacy of the assessed drug in relation to its comparator (C1 esterase inhibitor).

Considering the lack of basis to conclude that there are differences in the clinical effectiveness of the two therapies, an economic evaluation was performed using the cost minimisation technique. The economic analysis estimated that the use of icatibant instead of a human C1-esterase inhibitor leads to (trade secret) treatment of HAE attack.

On the other hand, a budget impact analysis for the reimbursement of Firazyr as part of a pharmacy list showed (trade secret) for the public payer.

It was also taken into account that, according to medical management guidelines, icatibant is one of the drug health technologies recommended for the treatment of acute HAE attacks in children.

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of public financing of a medicinal product:

- Firazyr, icatibantum, solution for injection, 10 mg/ml, 1, amp.-srn, EAN code 05909990740635 - net selling price (trade secret).

Proposed reimbursement payment and dispensing category: lump sum, drug available in pharmacies on prescription in an indication defined by a clinical condition, in an existing joint-limit group.

(trade secret)

Health problem

ICD-10 D84.1 Defects in the complement system; C1 esterase inhibitor (C1-INH) deficiency.

Angioedema is the swelling of the subcutaneous or submucosal tissue resulting from the dilatation and increased permeability of blood vessels, usually well-circumscribed, asymmetrical.

Hereditary angioedema (HAE) associated with the deficiency/decreased activity of C1-INH (C1-INH-HAE) – most cases are familial due to mutations in the gene encoding C1-INH located on chromosome 1 (isolated cases are de novo mutations).

- C1-INH-HAE type I – associated with plasmatic C1-INH deficiency (85% of HAE cases)
- C1-INH-HAE type II – associated with decreased C1-INH activity.

Type I, which occurs in 85% of patients with HAE, is characterised by low plasma C1-INH levels due to impaired C1-INH production as a result of multiple mutations in the gene.

Type II, in which plasma C1-INH levels are normal or increased but it is devoid of biological activity, occurs in the remaining 15% of patients with HAE.

The prevalence of HAE in the general population is approximately 1 in 50,000 with no known differences between ethnic groups.

The most recent Polish epidemiological data come from the National HAE Registry (2016), in which a total of 341 patients were registered. However, the registry does not include all centres providing HAE therapy in Poland; moreover, it is estimated that up to half of the patients may still be undiagnosed

Symptoms usually resolve without harm, but angioedema of the larynx and/or trachea is a life-threatening condition and remains the leading cause of death in this population. Before the advent of the therapy, the mortality rate associated with HAE was 30%.

In HAE, the swelling of the skin and mucous membranes is recurrent and occurs throughout life, often along with gastrointestinal symptoms. Each recurrence of symptoms is followed by several weeks of remission. Although INH C1-esterase deficiency is present at birth in HAE, the first symptoms usually appear in the first or second decade of life. Approx. 5% of patients with inhibitor deficiency have no clinical symptoms. Submucosal swelling of the throat, tongue, or larynx occurs at least once in a lifetime in approx. 50% of patients and it recurs repeatedly in some. Even the first incident of pharyngeal or laryngeal edema can cause acute respiratory failure and death.

Alternative health technology

Taking into account the clinical guidelines and technologies currently financed from public funds, the medicinal products Berinert (C1-esterase inhibitor) and Ruconest (conestat alfa) were indicated as comparators for the proposed technology.

Ruconest is not currently reimbursed.

Description of the benefit named in the application

Firazyr contains icatibant, which is a selective, competitive bradykinin type 2 (B2) receptor antagonist. It is a synthetic decapeptide with a structure similar to bradykinin but containing 5 non-proteinogenic amino acids. In HAE increased bradykinin concentrations are the key mediator in the development of the clinical symptoms.

According to the summary of product characteristics (SmPC), Firazyr is indicated for the symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents, and children aged 2 years and older with C1 esterase inhibitor deficiency.

The indication applied for is included in the registration indication.

Evaluation of efficacy (clinical and practical) and safety

This evaluation consists of collecting data on the health consequences (efficacy and safety) of a new therapy for a given health problem and other therapies that are currently publicly funded and represent alternative treatments available for the particular health problem. Subsequently, this evaluation involves determining the reliability of the collected data and comparing the efficacy and safety results of the new therapy against therapies that are already available for the treatment of the health problem in question.

Based on the above, the assessment of efficacy and safety provides an answer to the question of the measure of health outcome (in terms of both efficacy and safety) to be expected for the new therapy compared to other therapeutic options considered.

The target population in the application is children and adolescents aged 2 to 17 (up to the age of 18) with hereditary angioedema caused by C1 esterase inhibitor deficiency, in the event of acute life-threatening angioedema attacks.

No studies were found that would directly compare the proposed technology with selected comparators.

Clinical analysis included:

- A multi-centre single-arm study concerning icatibant for the symptomatic treatment of acute attacks of hereditary angioedema in 32 pediatric patients (Farkas 2017, abstracts: Farkas 2019, Kessel 2019);
- 7 publications on studies concerning the comparators:
    - of Berinert: Busse 2017, Schneider 2013 (IMPACT1/2 study), Farkas 2002, Farkas 2013, and Kreuz 2012;
    - of Ruconest: Baker 2017 and Reshef 2019.

Two systematic reviews were identified (Longhurst 2017, Pancholy 2019). Both present the results of the Farkas 2017 study.

The following primary endpoints were evaluated:

- time to onset of symptom relief *(TOSR)*, i.e. the earliest time after treatment when a 20% or greater improvement in the composite symptom score was achieved without the worsening of any single component score;
- time to minimum symptoms *(TTMS)*, i.e. time after treatment when all symptoms were mild or absent

The reliability of the single-arm study (Farkas 2017) was assessed using the NICE scale criteria. The score obtained was 7/8 points. In turn, the quality of included reviews without meta-analysis was considered critically low.

Efficacy

Firazyr (Farkas 2017)

Time to onset of symptom relief (TOSR):

- The median TOSR in the general population of the study was 1 hour (95% CI: 1.0; 1.1), with no significant differences between the predefined subgroups of children and adolescents;
- More than 70% of patients experienced symptom relief at 1.1 hours and more than 90% at 2 hours after icatibant administration.

Time to minimum symptoms (TTMS):

- The median TTMS in the general study population was 1.1 hours (95% CI, 1.0; 2.0). The results for the child population (1.9 hours; 95% CI, 1.0; 2.0) were similar to those of the adolescent population;

- Approximately 50% of patients reached minimum symptoms at 1 hour and 80% at 2 hours after treatment.

Overview of results

The presentation of results differed between studies for interventions and comparators. However, a summary of results for individual drug products was presented.

Median time to onset of symptom relief (TOSR):

- Firazyr (icatibant):
    - 1.00 hour (95% CI: 1.0; 1.1) – Farkas 2017 study
- Berinert (plasma-derived C1-esterase inhibitor):
    - 0.42 hours (range: 0.17-24.00) - IMPACT 1 study
    - 0.49 hours (range: 0.24-1.65) - IMPACT 2 study
- Ruconest (recombinant C1 esterase inhibitor):
    - 0.62 hours (95% CI: 0.52; 1.00) – calculated on the basis of the results of the Baker 2017 study
    - 1.00 hours (95% CI: 1.00; 1.08) – calculated on the basis of the results of the Reshef 2019 study

Median (95% CI) time to minimum symptoms (TTMS):

- Firazyr (icatibant):
    - 1.1 hour (95% CI:, 1.0; 2.0) – Farkas 2017 study
- Berinert (plasma-derived C1-esterase inhibitor): N/A
- Ruconest (recombinant C1 esterase inhibitor):
    - 1.93 hrs. (95% CI: 1.00; 2.35) – calculated on the basis of the results of the Baker 2017 study
    - 2.04 hrs. (95% CI: 2.00; 2.10) – calculated on the basis of the results of the Reshef 2019 study

In the Farkas 2017 study, twenty patients aged 4 or older were eligible for analysis by the Faces Pain Scale-Revised (FPS-R).

Two patients in the population eligible for efficacy evaluation were less than 4 years old and thus eligible for pain assessment using a scale designed for this age group that assesses faces, legs, activity, cry, and consolability symptoms (FLACC).

Pain assessment:

- On the FPS-R scale, the time to the reduction of pain symptoms amounted to 1.0 (95% CI: 0.8; 1.0) hours and the time to minimal symptoms was 3.4 (95% CI: 1.8; 5.3) hours. The baseline pain rating amounted to 5.4 (SD: 3.13). Improvement was noted within the first hour of the administration of icatibant (-3.0 [SD: 2.68]). The pain gradually decreased until the fourth hour after the administration of the drug, when its severity on the FPS-R scale reached 0.8 (SD: 1.64). The results were similar in the child and adolescent subgroups (median TTMS respectively: 2.4 hours [95% CI, 1.9-5.3] and 3.8 hours [95% CI, 1.0-6.8]);
- On the FLACC scale, one patient had a pre-treatment value of 0 and was excluded from the time-to-event analyses. For 1 eligible patient, TOSR and TTMS amounted to 1.0 hour.

Application of rescue therapy:

- one adolescent from the population eligible for safety assessment (but not for efficacy assessment) developed an HAE attack 6 hours after the use of icatibant. The patient received C1-INH as a rescue therapy;
- None of the patients included in the analysis of icatibant efficacy required rescue therapy within 48 hours of the administration of the drug.

Safety

In the Farkas 2017 trial, a total of 32 treatment emergent adverse events (TEAEs) were reported in 9 (28.1%) patients.

All of the TEAEs were mild or moderate. Gastrointestinal disorders were the most common (in 3 patients).

No severe TEAE or serious adverse events were reported after the treatment. No TEAEs led to discontinuation of the trial or death.

Most patients (90.6%) experienced injection site reactions, most commonly erythema (84.4%) and oedema (68.8%). Most injection site reactions were either mild or moderate.

Two patients (6.3%) had severe injection site reactions; both resolved 6 hours after dosing.

In relation to comparator safety (Berinert), adverse events (AEs) were reported in 14.3% of patients in the IMPACT1 trial and in 33.3% in IMPACT2 (the extension phase of the IMPACT1 trial).

The FDA Adverse Event Reporting System (FAERS) database (as of December 17, 2020) reported a total of 2,180 patients who developed adverse events while taking Firazyr, including 1,360 (62.4%) cases of serious adverse events (including deaths) and 77 (3.5%) deaths. The most commonly reported events were drug ineffectiveness, application site reactions, misapplication, laryngeal oedema, headache, nausea, pain and others.

Limitations

The main limitation of the reliability of the presented analysis is the lack of randomised trials directly comparing the assessed technology with the selected comparator in the applied population.

In addition, the uncertainty of the presented results of the clinical analysis is affected by the following aspects, among others:

- in the Farkas 2017 trial, it was not possible to assess life-threatening attacks (involving the pharynx, larynx or abdominal cavity) separately, as results were presented overall for recorded attacks (only one patient had 2 laryngeal attacks);
- lack of comparative trials allowing for classical indirect analysis by a common reference group for the applied population; comparison of icatibant efficacy with comparators (Berinert and Ruconest) was performed only by comparing the results for relevant subgroups treated with a given drug.

Proposed risk-sharing scheme

(trade secret)

Economic evaluation, including estimates of cost to health outcomes achieved

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with using the new therapy for an individual patient in place of already reimbursed therapies.

The costs of therapy are estimated in the currency of our country, and health outcomes are usually expressed in life-years gained (LYG) or quality-adjusted life years (QALY) as a result of the therapy.

By comparing the cost and outcome values of the new therapy to the costs and outcomes of already reimbursed therapies, one can answer the question of whether the health outcome achieved for an individual patient with the new therapy is associated with a higher cost compared to already reimbursed therapies.

The obtained results of the cost to health outcome ratio are compared with the use of the so-called break-even point, i.e. a result that indicates that given the wealth of our country (expressed in GDP), the maximum cost of the new therapy that is expected to produce a unit of health outcome (1 LYG or 1 QALY) compared to already available therapies should not exceed three times the GDP per capita.

Currently, the break-even point is PLN 155,514 (3 x PLN 51,838).

The cost to health outcome ratio does not estimate or determine the value of life, it only enables its assessment and, among others, on this basis, choose the therapy related to potentially the best outcome.

The cost-effectiveness evaluation included cost minimisation analysis within the time horizon of one acute HAE attack, from the perspective of the public payer - the entity obliged to finance the benefits from public funds, i.e.

the National Health Fund (NFZ) and from the joint perspective of the payer and the beneficiary. The results of the analysis from both perspectives were similar.

Only the costs of drugs used to treat HAE attack were included in the analysis.

According to the applicant's estimates, the use of Firazyr (trade secret)

Please note that the above estimates do not take into account a possible RSS for the drug Berinert.

None of the variants of the conducted sensitivity analysis changed the conclusions of the baseline analysis.

Limitations

The following aspects of the economic model, among others, influenced the uncertainty of the presented results:

- the lack of data to estimate the bodyweight of paediatric patients treated for acute HAE in Poland and therefore the lack of possibility to accurately estimate drug consumption;
- (trade secret)
- the analysis did not include the cost of administering the drugs (however, this approach is considered conservative).

Own calculations of the Agency

No additional own calculations were performed.

Indication whether the circumstances referred to in Art. 13 sec. of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Journal of Laws 2020, item 357 as amended);

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed in a particular indication, the official sales price of the drug must be calculated in such a way that the cost of use of the drug whose reimbursement is applied for is not higher than the cost of health technology with the most favourable ratio of obtained health outcome to the cost of obtaining them.

Due to the failure to present RCTs in the clinical analysis, the circumstances of Article 13 of the Reimbursement Act apply.

Own calculations of the Agency

The value of the official selling price of Firazyr at which the cost of its use is not higher than that of the comparator (Berinert) is:

- (trade secret)

Assessment of the impact on the healthcare system, including the impact on the budget of the public payer

The health system impact assessment has two major parts.

First, a payer budget impact analysis allows estimating the potential expenses associated with public funding of the new therapy.

Estimates of expenses associated with the new therapy (the "tomorrow" scenario) are compared to how much is currently spent on treating a health problem (the "today" scenario). On this basis, it is possible to assess whether a new therapy will require more resources to treat a given health problem or is associated with savings in the payer's budget.

A budget impact assessment determines whether the payer has adequate resources to fund a particular technology.

The assessment of health system impact in the second part answers the question of how the decision to fund the new therapy may affect the organisation of service delivery (particularly in the context of adjusting to the requirements of delivering the new therapy) and the availability of other healthcare services.

The results of the applicant's budget impact analysis are presented over a three-year horizon. The analysis was conducted from the perspective of the public payer (NFZ).

The analysis only included drug costs, while the other direct cost categories were considered non-differential.

The applicant has estimated the patient population that will use the proposed technology at:

- (trade secret)

The results of the base-line analysis (trade secret) indicate that the inclusion of the medicinal product Firazyr (icatibant) in the requested indication will entail (trade secret)

Limitations

The uncertainty of the presented results is affected by the following aspects:

- the analysis assumed the funding of the medicinal product Ruconest, which is currently not reimbursed;
- the estimation of the target population was conducted on the basis of epidemiological data.

Own calculations of the Agency

No additional own calculations were performed.

Comments on the proposed risk-sharing scheme

(trade secret)

Comments on the drug programme

Not applicable.

Discussion of the solutions proposed in the rationalisation analysis

The rationalisation analysis aims to identify a mechanism whose introduction will result in the release of public funds in an amount corresponding to at least the increase in costs resulting from a positive decision on reimbursement of the health technology named in the application.

A rationalisation analysis is submitted if the budget impact analysis for the entity responsible for funding shows an increase in reimbursement costs.

Not applicable.

Discussion of recommendations issued in other countries in relation to the assessed technology

Nine clinical recommendations related to the indication named in the application were found, issued by:

- Polskie Towarzystwo Alergologiczne (Polish Society of Allergology) (PTA 2018);
- European Society for Immunodeficiencies (ESID 2020);
- Australasian Society of Clinical Immunology and Allergy (ASCIA 2020);
- Canadian Hereditary Angioedema Network (CHAEN 2019);
- German Association of Scientific Medical Societies (GASMS 2019);
- World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI 2018);
- Hereditary Angioedema International Working Group (HAWK 2017);
- Hereditary Angioedema Association (HAEA 2016);
- French National Center for Angioedema (FNCA 2015).

The guidelines indicate that treatment of acute attacks should be immediate, also applied at home. The following options for the intravenous and subcutaneous treatment of attacks are provided: C1 complement inhibitor substitutes (Berinert, Cinryze) (intravenous), administration of recombinant C1 INH (Ruconest) (intravenous) or,

recommended because of its ease of use, blockade of the B2 receptor using a bradykinin receptor antagonist (Firazyr) (subcutaneous).

Treatment of HAE attacks should be started as soon as possible, especially in cases of oedema located in the upper respiratory tract, as they are life-threatening for the patient.

Reimbursement recommendations

Two positive recommendations (SMC 2018, AWMSG 2018) and one negative recommendation (NCPE 2013) were found. Positive recommendations mainly highlight the efficacy in the symptomatic treatment of acute attacks of hereditary angioedema in patients. In contrast, the negative recommendation advised against performing a full pharmacoeconomic assessment due to lack of data on the paediatric population in 2013.

According to the information provided by the applicant, the medicinal product Firazyr (icatibant) is financed in (trade secret) EU and EFTA countries (out of 31 indicated). (trade secret)

PRESIDENT

dr n. med. Roman Topór-Mądry

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Basis for the recommendation

The recommendation was prepared under an order dated 6 November 2020 of the Minister of Health (reference number: PLR.4500.827.2020.2.KK), regarding the preparation of the President's recommendation on the evaluation of the drug Firazyr (icatibant) for the indication: symptomatic treatment of acute, life-threatening attacks of hereditary angioedema in adolescents and children aged 2 years and older with C1 esterase inhibitor deficiency, pursuant to art. 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Journal of Laws 2020, item 357 as amended), upon receipt of the Position of the Transparency Board No. 10/2021 of 1 February 2021 on the evaluation of the drug Firazyr (icatibant) for the indication: symptomatic treatment of acute, life-threatening attacks of hereditary angioedema in adolescents and children aged 2 years and over with C1 esterase inhibitor deficiency

References

1. Position of the Transparency Board No. 10/2021 of 1 February 2021 on the evaluation of the drug Firazyr (icatibant) for the indication: symptomatic treatment of acute, life-threatening attacks of hereditary angioedema in adolescents and children aged 2 years and over with C1 esterase inhibitor deficiency
2. Report No. OT.4330.17.2020 Application for reimbursement of the medicinal product Firazyr (icatibant) in the indication: symptomatic treatment of acute, life-threatening attacks of hereditary angioedema in adolescents and children aged 2 years and over with C1 esterase inhibitor deficiency