Recommendation No. 145/2021
of 29 December 2021
of the President of the Agency for Health Technology Assessment and Tariff System
on Evrysdi (risdiplam) in the indication set out in the drug programme "Treatment of spinal muscular atrophy with risdiplam (ICD-10 G12.0, G12.1)"

The President of the Agency recommends the reimbursement of the following medicinal product:

- Evrysdi (risdiplam) powder for oral solution, 0.75 mg/ml, 1, bottle, 80 ml, EAN: 07613326029896

in the indication set out in the drug programme "Treatment of spinal muscular atrophy with risdiplam (ICD-10 G12.0, G12.1)" in a new limit group and supplying it free of charge **provided that**:

1. the annual cost of risdiplam is reduced to the level of the cost of nusinersen in one-year maintenance therapy;
2. the target population is limited to patients with SMA Types 1, 2, and 3 or pre-symptomatic individuals with the presence of up to three SMN2 copies;
3. a mechanism securing payer's budget is introduced to involve obligation for the applicant to reimburse the therapy of all patients included in the treatment in excess of the number of patients presented by the applicant in the basic scenario of the budget impact analysis;
4. the proposed drug programme is integrated with the currently reimbursed programme for the treatment of SMA with nusinersen.

Grounds for the recommendation

Evrysdi (risdiplam, RYS) is not currently reimbursed from public funds. According to the Summary of Product Characteristics, the product is indicated for the treatment of 5q spinal muscular atrophy

(SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.

In the population of patients with SMA Type 1, [information protected as a trade secret] In contrast, the group of patients with SMA Types 2 and 3 showed a significant prevalence of RYS over BSC in terms of endpoints (relative to the initial value): improvement in motor function on the MFM32 scale, score changes in the RULM scale and in the SMAIS scale as assessed by caretakers. There were no significant differences in terms of score changes in the HFMSE scale and SMAIS scale (assessment of patients ≥ 12 years). [information protected as a trade secret]

The efficacy of RYS in the pre-symptomatic patient population was assessed on the basis of of the ongoing RAINBOWFISH study. It has been shown that treatment results in the achievement of developmental milestones in all patients, and in the improvement in unsupported walking in the majority of patients (80%). However, reliable inference from this study is difficult due to the very small population (5 patients) included in the analysis.

Results of the JEWELFISH study indicate that the use of RYS after prior treatment is associated with stabilisation in motor function in the MFM32 scale at 12 months.

Safety analysis conducted on SMA Type 1 and Type 2/3 patient populations showed no significant differences in terms of incidence of adverse events between risdiplam and nusinersen. There were 6 deaths in the subpopulation with SMA Type 1 during the 24-month follow-up period. The most common serious adverse event was pneumonia, which was found in more than 30% of patients. In the SMA Type 2/3 group, there were no statistically significant differences in total adverse events between patients using RYS and BSC. No treatment-related serious adverse events were reported in any patient group. An indirect comparison of RYS vs NUS showed no statistically significant differences in the incidence of serious adverse events overall in SMA Type 2/3 patients. The safety profile in the subgroup of pre-symptomatic and pre-treated patients was also favourable; however, due to the very limited population, it is not easy to draw any conclusions.

The results of applicant's economic analysis, both from the perspective of the public payer and joint perspective, in [information protected as a trade secret]

[information protected as a trade secret]

The uncertainty of inference from economic analysis concerns in particular [information protected as a trade secret]
The limitations of the analyses are also due to the lack of high-quality efficacy data, comparative data and especially long-term data, which necessitates extrapolation of results over a much longer time horizon than available in the studies. Assumptions regarding the extrapolation of data have a significant impact on the results obtained, which reduces their reliability in the absence of data for the period. [information protected as a trade secret]

There were five reimbursement recommendations found for Evrysdi (risdiplam), including 2 positive ones (GBA 2021, Germany and NICE 2021, Great Britain;), 1 conditionally positive (CADTH 2021, Canada) and recommendations with two positive and negative decisions depending on the characteristics of the target population (HAS 2021, France; PBAC 2021, Australia).

Due to the very high unit costs, the RSS proposed by the applicant does not ensure cost-effectiveness and does not secure payer's expenditure in view of possible underestimation/overestimation of the target population. It is therefore required to deepen the terms of the risk-sharing scheme so that the applicant takes more responsibility for the financial risks of a possible positive reimbursement decision. The President of the Agency supports the suggestion of the Transparency Council to change

the scope of the risk-sharing scheme, i.e. to lower the annual cost of risdiplam to the level of the cost of nusinersen in one-year maintenance therapy, and to introduce a maximum level of payer's expenditure, above which the applicant will have to reimburse the therapy of all patients included in the treatment in excess of the number of patients presented by the applicant in the base-case scenario of the payer's budget impact analysis.

Furthermore, bearing in mind that drawing conclusion regarding the efficacy of the assessed technology based on the available scientific evidence is subject to uncertainty (among other things, due to the indicated limitations of the analyses performed), the President of the Agency considers it reasonable to limit the target population to patients with SMA Types 1, 2, and 3 or pre-symptomatic individuals with the presence of up to three SMN2 copies, which is also argued by the Transparency Council in its position paper.

Taking account of the above-mentioned limitations, it is considered appropriate to reimburse Evrysdi (risdiplam) in the indication defined in the drug programme "Treatment of spinal muscular atrophy with risdiplam (ICD-10 G12.0, G12.1)", in a new limit group and to dispense it free of charge provided that

1. the annual cost of risdiplam is reduced to the level of the cost of nusinersen in one-year maintenance therapy;
2. the target population is limited to patients with SMA Types 1, 2 and 3 or pre-symptomatic individuals with the presence of up to a maximum of three SMN2 copies;
3. a mechanism securing payer's budget is introduced to involve obligation for the applicant to reimburse the therapy of all patients included in the treatment in excess of the number of patients presented by the applicant in the basic scenario of the budget impact analysis;
4. the proposed drug programme is integrated with the currently reimbursed programme for the treatment of SMA with nusinersen.

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of public reimbursement of the following medicinal product:

- Evrysdi (risdiplam), powder for oral solution, 0.75 mg/ml, 1, bottle
  80 ml, EAN: 07613326029896, proposed net sales price is: [information protected as a trade secret]

in the indication: under the new drug programme “Treatment of spinal muscular atrophy with risdiplam (ICD-10 G12.0, G12.1)”.

Proposed reimbursement and dispensing category: level of payment for the patient - free of charge, under the drug programme (PL), in a new limit group. [information protected as a trade secret]

Health problem

Spinal muscular atrophy (SMA) is a genetic disease which involves damage to peripheral nervous system components responsible for skeletal muscle function.

In the spine, in the anterior horns of the spinal cord, there are cells called motor neurons that control the skeletal muscles. In SMA, these neurons stop transmitting impulses to the muscles. As a result of prolonged lack of stimulation, muscles decline, which is referred to as atrophy. SMA is classified as a neuromuscular disease. The most common type of SMA is associated with a deficiency of a protein essential for the survival of motor neurons (SMN). That protein determines neuronal survival; the higher the level of SMN protein in the body, the milder the symptoms of SMA. This protein is formed

by intracellular processes and cannot be supplied from outside. SMN protein deficiency in the body is caused by the mutation on the fifth chromosome in the main gene responsible for encoding SMN protein. This gene is referred to as SMN1.

SMA is divided into four types:

- Type I (SMA 1) is the most severe and common form. It manifests in early infancy and even in prenatal period. The infant has difficulty breathing, sucking, swallowing and is unable to hold his or her head upright, roll over to the side or sit without support. The patient requires palliative care, respiratory support, proper management of choking, artificial nutrition;
- Type II (SMA 2) usually manifests between 6 and 18 months of age. In this form of the disease, weakness and atrophy occurs first in the proximal muscles (those closer to the torso), followed by the distal muscles (those further away from the torso). The main cause of risk is the weakening of the muscles responsible for breathing, thus pulmonological care is essential. It may be necessary to introduce temporary or permanent respiratory support, usually non-invasive one. A curvature of the spine (usually scoliosis) can develop very early;
- Type III (SMA 3) manifests in childhood and adolescence and is characterised by a diversity of symptoms. Patients are able to walk without assistance until the third or fourth decade of life (Type 3b), but sometimes they lose their ability to walk in early childhood (Type 3a);
- Type IV (SMA 4) occurs in adulthood, usually in the fourth or fifth decade of life. In this type, the course of disease is the mildest - patients usually only experience difficulty walking.

There is also Type 0 (prenatal) differentiated in some studies.

In Poland, one in 35 people, which represents around one million inhabitants of our country, is a carrier of a mutation that may cause SMA. On average, one in 7,000 children born will develop spinal muscular atrophy. Annually, around 50 children are diagnosed with the disease, and in around 35 of them the disease has a severe form. As on 14 December 2021, the records of the Polish Registry of Patients with SMA maintained by the Department of Neurology at Medical University of Warsaw include 841 people with SMA (SMA Type 1=177 patients; SMA Type 2=228 patients; SMA Type 3=422 patients; SMA Type 4=14).

Experts surveyed by the Agency estimate that the current number of SMA patients in Poland is in the range of 150- 200 (SMA Type 1); 650-750 (SMA Type 2 and SMA Type 3) and the number of new cases per year amounts to 24-40 (SMA Type 1) and 25-35 (SMA Type 2 and SMA Type 3).

A newborn screening programme for SMA is being implemented in Poland in stages (from April 2021 to autumn 2022). The programme is likely to increase the detectability of SMA in Poland.

The mortality rate is dependent on the patient's age at which the first symptoms occurred. High mortality is associated with the early onset of the disease. For SMA Type 1, median survival is 7 months with a mortality rate of 95% by the age of 18. Patients with SMA Type 2 live to adulthood in most cases. The life expectancy of people with mild SMA is not different from the average.

Alternative health technology

The applicant has identified Spinraza (nusinersen) as an alternative technology to Evrysdi (risdiplam) reimbursed under B.102 drug programme. “Treatment of spinal muscular atrophy (ICD-10 G12.0, G12.1)”. Moreover, as some patients are not eligible for the drug programme, best supportive care (BSC) was identified as a second comparator. The choice of the comparator was considered reasonable.

Description of the proposed intervention

Risdiplam is a pre-mRNA folding modifier of the survival motor neuron gene 2 (SMN2) developed to

treat SMA caused by alterations in SMN1 gene on chromosome 5q that lead to SMN protein deficiency. Deficiency of functional SMN protein is directly linked to the pathophysiology of SMA, which includes progressive loss of motoneurons and muscle weakness. Risdiplam corrects SMN2 folding to shift the balance from skipping exon 7 towards including exon 7 in the mRNA transcript, leading to increased production of functional and stable SMN protein.

In accordance with the Summary of Product Characteristics (SmPC), Evrysdi (risdiplam) is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients aged 2 months and older with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or those who have one to four SMN2 copies.

The proposed reimbursement indication of Evrysdi in the proposed drug programme "Treatment of spinal muscular atrophy with risdiplam (ICD-10 G 12.0, G12.1)" covers treatment of spinal muscular atrophy 5q (SMA) in patients aged 2 months and older with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or those who have one to four SMN2 copies. In the case under consideration, the proposed population corresponds to the registered indication.

Efficacy, effectiveness and safety assessment

This assessment involves collecting data on the health consequences (efficacy and safety) of the new therapy for the health problem in question and of other therapies that are currently reimbursed from public funds and represent alternative therapies available for the health problem. Furthermore, this assessment requires determination of the reliability of data collected and a comparison of the efficacy and safety results of the new therapy against the therapies already available to treat the health problem in question.

On the basis of the above, the efficacy and safety assessment allows answering the question of the scale of the health outcome (both in terms of efficacy and safety) to be expected from the new therapy compared with other therapeutic options under consideration.

As no studies directly comparing RYS and NUS were found, an indirect comparison was made. The applicant's systematic review included 4 primary studies meeting the inclusion criteria for risdiplam.

- SUNFISH (Mercuri 2018_poster, Mercuri 2020_poster, Day 2020_poster, Day 2021_poster, NCT02908685, [information protected as a trade secret] - randomised, double-blind, multicentre, phase 2/3 study. The intervention involved the administration of risdiplam (RYS), with best supportive care (BSC) as the comparator. The population included patients with SMA Type 2/3. The total number of patients in the part of the study included in the analysis was N=180 (RYS n=120; BSC n=60). Follow-up period: 12 months, 24 months data on the natural history of disease.
- FIREFISH (Servais 2020_poster, Darras 2021, Baranello 2021, Servais 2020_poster, NCT02913482, [information protected as a trade secret] Darras 2021_poster, Darras 2021_prez.)
  – single-arm, experimental, prospective multicentre, open-label, phase 2/3 study. RYS was the intervention in the study. The population comprised patients with SMA Type 1. The number of patients in the part of the study included in the analysis was N=41. Follow-up period in the study: 24 months.
- JEWELFISH (Chiriboga 2020_poster, Chiriboga 2021_prez, NCT03032172, [information protected as a trade secret]
  – single-arm, experimental, prospective, multicentre, open-label, phase 2 study. RYS was the intervention in the study. The population consisted of pre-treated SMA patients. The total number of patients included in the study was N=174, including groups of patients pre-treated with nusinersen n=76. Follow-up period: [information protected as a trade secret] [information protected as a trade secret]
- RAINBOWFISH (Finkel 2021_poster, Finkel 2021_prez, Servais 2021_poster, NCT03779334)

– single-arm, experimental, prospective, multicentre, international, open-label, phase 2 study. RYS was the intervention in the study. The clinical population consisted of children aged up to 6 weeks with pre-symptomatic SMA. The number of patients was N=12. The efficacy results are presented only for patients treated with RYS for at least 12 months n=5. The study has an ongoing status.

Primary studies for nusinersen were also included in the analysis: [information protected as a trade secret]

Moreover, the applicant identified 2 systematic reviews:

- Wadman 2019 - relating to patients with SMA Type 1,
- Wadman 2020 - relating to patients with SMA Type 2/3,

The Agency Verification Analysis did not present the results of the above-mentioned reviews, as they do not concern the assessment of the efficacy and safety of the proposed technology.

Cochrane risk-of-bias assessment for SUNFISH for all domains analysed was determined to be low, for studies [information protected as a trade secret] for the domain hiding the randomisation code as unknown, in others - low.

Single-arm studies were assessed using the NICE scale. FIREFISH scored 7/8 (no information on the order of patient inclusion), JEWELFISH scored 7/8 (no information on the order of patient inclusion), and RAINBOWFISH scored 5/8 (no results in subgroups, no indication of consecutive patient recruitment, study results not clearly described, no full-text publication).

Efficacy [information protected as a trade secret]

[information protected as a trade secret]

<u>SMA Types 2 and 3 RYS vs BSC - direct comparison (SUNFISH)</u>

- Improvement in MFM32 score - comparison of RYS and BSC in terms variation in MFM32 score against initial value indicates improvement in motor function after RYS treatment. The result reached statistical significance, MD=1.55 (95% CI: 0.30, 2.81; p=0.0156).

  Results of the comparison indicate that RYS-treated patients were statistically significantly more likely to experience stabilisation (a change in MFM32 score of ≥0) and improvement in the score (in SUNFISH, a change in score of ≥3 points meant a large improvement) on the MFM32 scale compared to the control group:

  - Change in MFM32 score by ≥3 points as compared to the initial value. OR=2.35 (95% CI: 1.01; 5.44; p=0.047).
  - Change in MFM32 score by ≥0 points as compared to the initial value. [information protected as a trade secret]
- Improvement in RULM score - there was a statistically significant difference in favour of RYS versus BSC in terms of change in RULM score as compared to the initial value, MD = 1.59 (95% CI: 0.55; 2.62; p=0.003).
- Improvement in HFMSE score - statistical analysis conducted for the change in HFMSE score as compared to the initial values showed no statistically significant differences between RYS and BSC. (MD=0,58 (95%CI [information protected as a trade secret], p=0,3).
- Improvement in SMAIS score as compared to the initial values - in RYS group compared to BSC, statistically significant improvement in patient independence as assessed by caretakers MD=

[information protected as a trade secret], p=0.002) was demonstrated, yet in the assessment of patients themselves the result did not reach statistical significance, MD = [information protected as a trade secret]

SMA Types 2 and 3 –

[information protected as a trade secret]

SMA Type 1/3 - pre-treated patients (JEWELFISH)

The application of RYS after prior NUS treatment is associated with stabilisation in motor function as assessed on the MFM32 scale over the period of 12 months (Chiribog 2021 presentation as part of JEWELFISH).

Patients diagnosed with SMA - pre-symptomatic patients (RAINBOWFISH)

- Motor function assessment in the HINE-2 scale - improvement in functions:
  - head control, sitting, turning and crawling were achieved by 100% of patients (N=5);
  - standing with support was achieved by 20% of patients (n=1);
  - unsupported standing was achieved by 80% of patients (n=4);
  - walking, creeping up was achieved by 20% of patients (n=1);
  - unsupported walking was achieved by 80% of patients (n=4).
- Motor function assessment in the CHOP-INTEND scale - maximum score (i.e.: 64 points) was achieved by 80% of patients (n=4); a score of 63 points was achieved by 20% of patients (n=1). All patients (N=5) reached a score of at least 60.

Safety

SMA Type 1 (FIREFISH)

- Deaths - reported in 10.3% of patients (6/58);
- Serious adverse events - reported in 69% of patients (40/58), the most common being pneumonia in 34.5% of patients.
- Adverse events - occurred in all patients included in the study. The most commonly reported adverse events were upper respiratory tract infections (in about 55% of patients), fever (in about 53% of patients) and pneumonia (in about 40%).
- Treatment-related adverse events - reported in approximately 14% of patients (8/58).

There were no reported adverse events leading to treatment discontinuation, adverse events leading to dosage variations and/or discontinuation of the medication. [information protected as a trade secret]

SMA Types 2 and 3 RYS vs BSC (SUNFISH)

- Deaths - no deaths were reported in any of the groups.
- Treatment-related adverse events -
  - there were no statistically significant differences between the groups reported.
- Serious adverse events and treatment-related serious adverse events
  no statistically significant differences between RYS and BSC in terms of the incidence of serious adverse events were demonstrated.

No treatment-related serious adverse events were reported in any of the patient groups.

A statistically significant difference among serious adverse events was noted only for pneumonia RD=0.06 (95% CI: 0.001; 0.12) NNH=16 (95%CI: 8; 1.000)) in the absence of IS parameter OR=4.78 (95% CI: 0.59; 38.68). [information protected as a trade secret]

SMA - pre-symptomatic patients (RAINBOWFISH)

- Deaths - no deaths were reported.
- Serious adverse events - One serious adverse event was reported (gastroenteritis of norovirus aetiology). This event was not classified as a RYS treatment event.
- Adverse events - reported in 83% of patients. An adverse event reported in 1 patient with >2 SMN2 copies led to dosage change/discontinuation of medication. The most common adverse events included nasal congestion (about 33% of total patients), cough (about 25% of total patients) and teething (about 25% of total patients).

SMA - pre-treated patients (JEWELFISH: Chiriboga 2021 prez)

- Deaths - no deaths were reported.
- Adverse events - reported in approximately 92% of patients overall. The most common adverse event was upper respiratory tract infection (about 17% of patients).
- Treatment-related adverse events in general were reported in about 19% of patients. There was no case of exclusion from the study due to treatment-related adverse events.
- Serious adverse events were reported in about 14% of patients.

Information based on SmPC

According to the SmPC, the most common adverse effects related to Evrysdi include:

- fever (54.8%), rash (29.0%) and diarrhoea (19.4%) - patients with the infantile onset of SMA
- fever (21.7%), headache (20.0%), diarrhoea (16.7%) and rash (16.7%) - patients with SMA of later onset.

Information based on safety communications regarding Evrysdi on the websites of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL), the European Medicines Agency (EMA) and Food and Drug Administration (FDA)

No resources (adverse event reports) regarding the safety profile of the evaluated intervention were found on the EMA, URPL and FDA websites. [information protected as a trade secret]

[information protected as a trade secret]

Limitations

The main limitations of the clinical analysis are those related to the following aspects:

- No studies containing a direct comparison of RYS against NUS;
- The risdiplam study is still in progress, so the results cannot yet be considered final;
- It is not possible to compare RYS and NUS over a longer follow-up period due to lack of results for the comparator over 24 months;
- Conclusions on the efficacy of risdiplam in the SMA Type 1 patient population are based on FIREFISH which is a single-arm study. Hence, it is not possible to carry out an indirect comparison by a common comparator with [information protected as a trade secret]

- Pre-treated patients were excluded from SUNFISH and FIREFISH and, at the same time, the applicant waived the presentation of the efficacy outcome of RYS therapy in pre-treated patients available in the Chiriboga 2021 (JEWELFISH) presentation;
- Patients who were able to walk independently were excluded from [information protected as a trade secret] and SUNFISH. This criterion is narrower than the inclusion criteria for the draft drug programme; [information protected as a trade secret]

A detailed description of limitations is presented in the Agency Verification Analysis. [information protected as a trade secret]

Economic evaluation, including a cost-effectiveness estimation

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with the administration of the new therapy to an individual patient instead of already reimbursed therapies.

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

Juxtaposing the values concerning the costs and outcomes of a new therapy and comparing them to the costs and outcomes of already reimbursed therapies allows answering the question of whether the health outcome achieved in an individual patient owing to a new therapy is associated with a higher cost in comparison with already reimbursed therapies.

The obtained results of the cost-effectiveness ratio are compared with the so-called cost-effectiveness threshold, i.e. a result that indicates that given the wealth of Poland (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 GDP per capita.

Currently, the cost-effectiveness threshold is PLN 166,758.00 (3 x PLN 55,586.00)

The cost-effectiveness ratio does not estimate or determine the value of life, but it only enables its assessment and on that basis, among other things, choosing the therapy related to potentially best outcome.

The aim of the analysis is to assess the cost-effectiveness of Evrysdi (risdiplam) for the treatment of spinal muscular atrophy (SMA) (the population is SMA 5q patients aged 2 months and older, with one to four SMN2 copies or with a clinical diagnosis of SMA Type 1, 2 or 3).

The economic analysis was performed separately for the SMA Type 1 and SMA Type 2 and 3 populations using a utility cost technique in comparison with the best supportive treatment (BSC) and the currently reimbursed drug programme - nusinsersen (NUS), from a public payer (NFZ - National Health Fund) and joint (NFZ and patient) perspective. Having regard to the way the drug is reimbursed (i.e. the drug programme), the results in both of the above perspectives are the same. The analysis assumed [information protected as a trade secret]

Different cost categories (cost of drugs; cost of prescribing and administering drugs; costs of diagnosis, monitoring and assessment of treatment effectiveness; costs of qualifying patients for the drug programme; costs of hospitalisation; costs of physiotherapy, rehabilitation and nutrition; costs of nursing and care services in long-term care; costs of medical devices; costs of palliative treatment). [information protected as a trade secret]

The applicant has carried out a one-way sensitivity analysis through an extreme value analysis, scenario analysis and probabilistic analysis.

Extreme value analysis [information protected as a trade secret]

Scenario analysis [information protected as a trade secret]

Probabilistic sensitivity analysis (PSA) [information protected as a trade secret]

Agency's own calculations [information protected as a trade secret]

Limitations

The main limitations to the analysis are related to following issues: [information protected as a trade secret]

[information protected as a trade secret]

- There are no high quality efficacy data, comparative data and especially long-term data, which necessitates extrapolation of results over a much longer time horizon than available in the study, and which may reduce the reliability of the results obtained.

A detailed description of limitations is presented in the Agency Verification Analysis.

Indication whether the circumstances referred to in Art. 13 sec. 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523 as amended) do arise.

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed, the official selling price of the drug must be calculated so that the cost of the drug to be reimbursed is not higher than the cost of the health technology with the most favourable cost–effectiveness ratio. [information protected as a trade secret]

Agency's own calculations [information protected as a trade secret]

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

Healthcare system impact assessment has two major parts.

First, the analysis of the impact on the payer's budget allows estimating the potential expenses associated with public reimbursement of the new therapy.

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

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

Healthcare system impact assessment in the second part answers the question of how the decision on the reimbursement of a new therapy may affect the organisation of the provision of services (particularly in terms of adaptation to the requirements of the implementation of the new therapy) and the availability of other healthcare services.

Budget impact analysis (BIA) was performed to estimate public payer's expenditure in the event of a favourable decision on the reimbursement from public funds of Evrysdi (risdiplam) for the treatment of spinal muscular atrophy 5q (SMA) in patients aged 2 months and older with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or having one to four SMN2 copies.

Assumptions of the analysis:

- the perspective of the entity obliged to reimburse interventions from public funds (public payer, NFZ) and additionally the joint perspective: NFZ and the beneficiary. The joint perspective is the same as the payer perspective;
- time horizon: 2 years (January 2022 to the end of December 2023);
- To compare the costs of RYS with NUS and BSC, direct medical costs (costs of drugs; costs of prescribing and administering drugs; costs of diagnosing, monitoring and assessment of treatment effectiveness; costs of qualifying patients for the drug programme; costs of hospitalisation; costs of physiotherapy, rehabilitation and nutrition; costs of nursing and care services in long-term care; costs of medical devices; costs of palliative treatment) were taken into account;
- population size: [information protected as a trade secret]

[information protected as a trade secret]

As part of the sensitivity analysis, the applicant conducted a one-way sensitivity analysis in the form of a extreme value analysis and scenario analysis.

Extreme value analysis [information protected as a trade secret]
Scenario analysis [information protected as a trade secret]

[information protected as a trade secret]

Agency's own calculations [information protected as a trade secret]

Limitations

[information protected as a trade secret]
[information protected as a trade secret]

The above assumptions translate into uncertainty of the inference of the BIA results.

A detailed description of limitations is presented in the Agency Verification Analysis. [information protected as a trade secret]

Comments on the drug programme

The Transparency Council pointed out the relevance of integrating the proposed drug programme with the currently reimbursed programme for the treatment of SMA with nusinersen.

Discussion on the solutions proposed in the rationalisation analysis

The subject of the rationalisation analysis is the identification of a mechanism, the introduction of which 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 the reimbursement of the health technology covered in this recommendation.

The rationalisation analysis is submitted if the budget impact analysis for the entity responsible for the reimbursement indicates an increase in reimbursement costs. [information protected as a trade secret]

Overview of recommendations in relation to the assessed technology

Clinical recommendations

Only one clinical guideline on pharmacotherapy applied in the treatment of SMA was found (Finkel

2018 - this document is an update of the 2007 guideline. Wang 2007). However, it does not refer to the use of Evrysdi, whereas the aforementioned guidelines were published in 2018 and Evrysdi was admitted to marketing in 2021.

Furthermore, one consensus of the European expert community was found (Kirschner 2020) which indicated that the currently available drugs that modify the course of the disease are Spinraza and Evrysdi. Gene replacement therapy with Zolgensma drug was identified as an alternative treatment pathway for SMA.

Reimbursement recommendations

Five reimbursement recommendations were found for Evrysdi (risdiplam; RYS):

- (GBA 2021, Germany) positive - the recommendation indicates that RYS can be effective in pre-symptomatic individuals;
- (NICE 2021, Great Britain) positive - the recommendation indicates that the use of RYS is associated with improved motor function in patients with SMA Type 1-3;
- (CADTH 2021, Canada) positive under certain conditions - the document indicates as a condition the reduction of the drug price and the use of the drug in patients aged from 2 months up to 25 years with documented two or three SMN2 copies;
- (HAS 2021, France) positive/negative - the recommendation was positive for the reimbursement of RYS in the population of SMA 5q patients aged 2 months and older with clinically confirmed SMA Type 1, 2 or 3, and negative for the reimbursement of RYS in the population of pre-symptomatic SMA patients with up to four SMN2 copies, due to the lack of efficacy data;
- (PBAC 2021, Australia) positive/negative - the document positively assesses decision to reimburse Evrysdi in the SMA Type 1, 2 or 3a in patient population aged ≤18 at treatment initiation, and negatively in the SMA Type 3b patient population aged ≤18 years at the start of treatment and SMA Type 1, 2 or 3 patients aged >18. [information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared on the basis of an Order of the Minister of Health of 12 October 2021 (ref. no.: PLR.4500.1268.2021.13.PBO), concerning the preparation of the President's recommendation on the assessment of Evrysdi (risdiplam), powder for oral solution, 0.75 mg/ml, 1, bottle, 80 ml, EAN: 07613326029896, in the indication specified in the drug programme "Treatment of spinal muscular atrophy with risdiplam (ICD-10 G12.0, G12.1)", 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 (Dz. U. /Journal of Laws/ of 2021, item 523 as amended), having obtained Position of the Transparency Council No. 145/2021 of 27 December 2021 on the assessment of Evrysdi (risdiplam) under the drug programme “Treatment of spinal muscular atrophy with risdiplam (ICD-10 G12.0, G12.1)”

References

1. Position of the Transparency Council No. 145/2021 of 27 December 2021 on the assessment of Evrysdi (risdiplam) under the drug programme “Treatment of spinal muscular atrophy with risdiplam (ICD-10 G12.0, G12.1)”
2. Verification Analysis No. OT.4231.52.2021 “Application for reimbursement of Evrysdi (risdiplam) under the drug programme »Treatment of spinal muscular atrophy with risdiplam (ICD-10 G12.0, G12.1)«”. Completion date: 17 December 2021.