Recommendation No. 123/2021

of 12 November 2021

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

on the assessment of Tysabri (natalizumab) in the indication set out in the drug programme "B.46. Treatment of multiple sclerosis [information protected as a trade secret] or primary progressive multiple sclerosis (ICD-10 G 35)"

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

- Tysabri (natalizumab), solution for injection, 150 mg, 2, pre-filled syringe containing 1 ml solution, GTIN code: 05713219560252

in the indication defined in the drug programme "B.46. Treatment of multiple sclerosis [information protected as a trade secret] or primary progressive multiple sclerosis (ICD-10 G 35)" in the existing limit group and dispensing it free of charge **provided that [information protected as a trade secret].**

Grounds for the recommendation

Tysabri (natalizumab) is currently financed under the B.46 drug programme for intravenous administration (IV). The application under assessment is for natalizumab for subcutaneous administration (S.C.) and is intended to be another option for the treatment of multiple sclerosis.

The applicant made a direct comparison between natalizumab S.C. and natalizumab IV based on RCTs (REFINE, DELIVER) in the analyses. Efficacy and safety assessments were presented for a patient population previously treated with natalizumab (REFINE) and a patient population previously not treated with natalizumab (DELIVER). In conclusion, the results of the included RCTs indicate a comparable efficacy and safety profile of natalizumab administered subcutaneously versus natalizumab administered by intravenous infusion. In the population of patients previously treated with natalizumab, there were no statistically significant differences in the endpoints: total number of unique active lesions in MRI; proportion of patients meeting emergency treatment eligibility criteria for MRI lesions; relapse; disability deterioration, and no statistical analysis of the aforementioned results was available for the assessment of the annualised relapse rate. In the population of patients who were not previously treated with natalizumabno statistically significant differences were reported for the following endpoints: annualised relapse rate; assessment of cognitive functions, visual impairment and general well-being; MRI lesions. When assessing disability, there were no statistically significant differences between the groups in the Multiple Sclerosis Functional Composite (MSCF), but a statistically significant higher degree of disability was reported for the natalizumab IV group compared to the natalizumab S.C. group in the EDSS (Expanded Disability Status Scale).

The safety profile of natalizumab in both forms, as assessed by the studies mentioned above, was similar and the differences were not statistically significant (except for a significantly lower risk of nervous system disorders and headaches).

There are no data on effectiveness. It should also be noted that the proposed drug programme concerns the population aged 12 and older, whereas the studies included in the analysis cover adult patients only. Therefore, it is not possible to determine the efficacy of the assessed technology in the population of patients aged 12-17.

According to the results of the economic analysis from both the public payer and joint perspective, the application of natalizumab SC administered subcutaneously instead of natalizumab IV administered intravenously [information protected as a trade secret] The limitations of the clinical analysis result in the uncertainty of the conclusions based on the economic analysis, in particular of the assumptions on the choice of the analytical method and the financing of the technology in question.

According to the information at https://polpharmabiologics.com/pl/portfolio-i- co-production/products-biosimilars, a biosimilar of natalizumab in intravenous form is currently being studied in Poland. This information may be of importance in the process of negotiating reimbursement and pricing conditions.

The budget impact analysis showed that [information protected as a trade secret] of the expenditure of a public payer [information protected as a trade secret] result from a lower cost of administering natalizumab subcutaneously to the patient. Sensitivity analysis indicates that if the costs of administering both drug forms are equalised, the reimbursement of natalizumab S.C. will have a neutral impact on the budget. Furthermore, the analysis is limited by the applicant's assumptions regarding the estimation of the target population.

No reimbursement recommendations have been identified for the application of the technology in question (natalizumab administered subcutaneously).

In summary, it should be noted that the conclusions regarding the efficacy of the assessed technology based on available scientific evidence will be burdened with uncertainty. Based on the available data, the therapy of the population treated with natalizumab will most probably be neutral budget-wise. According to expert opinions, the application of the subcutaneous form of the drug will be beneficial for both medical staff and patients, due to the more convenient and less burdensome procedure of administering the drug in the SC form compared to the IV form. Therefore, taking into account the position of the Transparency Council, in particular the lack of long-term data on the efficacy and safety of the new form of administration of natalizumab, it is considered reasonable to publicly finance the therapy provided that [information protected as a trade secret]

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:

- Tysabri (natalizumab), solution for injection, 150 mg, 2, pre-filled syringe containing 1 ml of solution, GTIN code: 05713219560252, the proposed net sales price is: [information protected as a trade secret]

in the indication: under the drug programme "B.46 Treatment of multiple sclerosis [information protected as a trade secret] or primary progressive multiple sclerosis (ICD-10 G 35)".

Proposed payment and dispensing category: patient - free of charge, under the drug programme, in existing limit group 1116.0 Natalizumab.
[information protected as a trade secret]

Health problem

Multiple sclerosis (MS) (Latin sclerosis multiplex) is a chronic, inflammatory-demyelinating immune-

mediated disease. It is characterised by a multifocal and diffuse temporal formation of lesions in the central nervous system that lead to axonal loss. The course of the disease can be variable, but it systematically leads to neurological deterioration in patients and is the most common non-traumatic cause of permanent disability in young people. The following clinical forms of multiple sclerosis are distinguished:

- relapsing-remitting multiple sclerosis (RRMS);
- secondary progressive multiple sclerosis (SPMS);
- primary progressive multiple sclerosis (PPMS);
- progressive-relapsing multiple sclerosis (PRMS).

The number of MS patients in Poland is estimated at approx. 45,000. It has been estimated that relapsing-remitting multiple sclerosis (RRMS) occurs in approximately 80% of patients. People aged 20-40 are most likely to suffer from MS. The disease reduces life expectancy by an average of 6-7 years. Death can occur as a result of disease complications associated with neurological symptoms and immobilisation.

Alternative health technology

The following disease-modifying drugs are publicly funded under the B.46 drug programme:

- in the population of patients with relapsing-remitting multiple sclerosis [information protected as a trade secret] natalizumab (as a concentrate for infusion solution), fingolimod, alemtuzumab, ocrelizumab and cladribine;
- in the population of patients with relapsing-remitting multiple sclerosis [information protected as a trade secret] natalizumab (as a concentrate for infusion solution), fingolimod, alemtuzumab and cladribine.

Among the above drugs currently funded in the B.46 drug programme, the applicant adopted natalizumab administered intravenously as a comparator. The choice of the comparator was considered reasonable.

Description of the proposed intervention

Natalizumab is a selective adhesion molecule inhibitor that binds to the α4 subunit of human integrin, which is highly expressed on the surface of all leukocytes except neutrophils. Natalizumab binds specifically to integrin α4β1, blocking the interaction with its receptor, vascular intercellular adhesion molecule 1 (VCAM-1) and ligands - osteopontin and the alternatively formed fibronectin domain - connecting segment 1 (CS-1). Natalizumab blocks the interaction of integrin α4β7 with mucosal vascular addressin cell adhesion molecule 1 (MadCAM-1).

Natalizumab may have a suppressive effect on the ongoing inflammatory process at the affected site and inhibit further development of inflammatory cells in the inflamed tissue.

According to the Summary of Product Characteristics (SmPC), Tysabri (natalizumab) is indicated for use in adult patients as monotherapy for disease modification in relapsing-remitting multiple sclerosis in the following patient groups:

1. with highly active disease despite a full and adequate course of treatment with at least one disease-modifying therapy (DMT) or
2. with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

The proposed reimbursement indication for Tysabri (natalizumab) includes the treatment of relapsing-remitting multiple sclerosis [information protected as a trade secret] The B.46 drug programme applies to the population aged 12 and over and according to the SmPC, Tysabri is

indicated in adult patients with relapsing-remitting multiple sclerosis. [information protected as a trade secret].

[information protected as a trade secret].

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.

The applicant's systematic review included two RCTs of the assessed technology:

- REFINE (Trojano 2021) – a phase II study directly comparing natalizumab subcutaneously (SC) administered with natalizumab intravenously (IV) administered in patients with RRMS who have previously received natalizumab IV treatment. Total number of patients in the study N=290, including natalizumab SC (300 mg every 4 weeks) group n=45, natalizumab IV (300 mg every 4 weeks) group n=54, which are the subject of this analysis. Follow-up period: 72 weeks, including a 60-week randomised, blinded phase of the study and a 12-week follow-up period in which all patients received natalizumab IV at 300 mg every 4 weeks.
- DELIVER (Plavina 2016) – a phase I study providing a direct comparison of natalizumab SC with natalizumab IV used in patients with RRMS or secondary progressive multiple sclerosis (a subpopulation of RRMS patients was identified) not previously treated with natalizumab. Number of patients: in natalizumab SC group (300 mg every 4 weeks) n=12, in natalizumab IV group (300 mg every 4 weeks) n=12. Follow-up period: for RRMS – 32 weeks (phase I [single dose of natalizumab, pharmacokinetic *(*PK) and pharmacodynamic (*PD*)] analysis – 8 weeks; phase II – 24 weeks).

in addition:

- 2 unpublished studies described in 5 references: NCT02142192, NCT03689972 – studies did not include the results of the efficacy or safety of Tysabri;
- studies included in the additional safety assessment (reports on natalizumab IV were also included): SmPC of Tysabri, the European Public Assessment Report (EPAR) for natalizumab, recommendations issued by the EMA on the safety of natalizumab [EMA recommendations], communication on the risk of progressive multifocal leukoencephalopathy (PML) associated with natalizumab use issued by the FDA [FDA 2018], natalizumab safety data collected in the FAERS adverse event reporting system of the FDA [FDA FAERS 2020], adverse event reports published on the Netherlands Pharmacovigilance Centre Lareb website [LAREB 2021], information on healthcare professionals on the safety of natalizumab in the context of the risk of PML published on the Health Canada website [Health Canada 2010], information on updates to measures to minimise the risk of PML during natalizumab treatment [URPL 2016] and references to EMA recommendations on the safety of natalizumab [EMA PRAC recommendations] published on the website of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPLWMPB). [information protected as a trade secret]

Cochrane risk-of-bias assessment for REFINE and DELIVER showed unclear risk of bias for most domains. It is worth mentioning that for the DELIVER study, a high risk of bias was reported for the following domains: blinding of participants and medical staff and blinding of endpoint assessors. In contrast, for the REFINE study, a high/unclear risk of bias was reported for the following domains:

randomisation method and randomisation mode – allocation concealment.

Efficacy

Efficacy assessments were presented for the population of patients previously treated with natalizumab based on the REFINE study and for the population of patients previously not treated with natalizumab based on the DELIVER study. A summary of the results in terms of the analysis of pharmacokinetic and pharmacodynamic profile is also presented.

Population of patients previously treated with natalizumab (REFINE study)

Efficacy was evaluated for the following endpoints:

- The total number of unique active lesions in a *Magnetic Resonance Imaging* (MRI) The study showed that in the 60th week of follow-up, the total number of unique active lesions (primary endpoint) in the natalizumab SC treatment group (0.02) was comparable to the number of lesions recorded in the natalizumab IV group (0.23) – no statistically significant differences were found between the groups analysed.

  Results of a *post-hoc* analysis adjusted for baseline T2 lesion volume showed that over a treatment period of 60 weeks, the estimated mean number of total unique active lesions was 0.035 [95% CI: 0.002; 0.567] in the study group and 0.209 [95% CI: 0.032; 1.372] in the control group. The difference was not statistically significant.

  After 60 weeks of treatment, one patient in the study group and 4 patients in the control group showed ≥1 total unique active lesion from baseline. The proportion of patients with any of the above lesions was 0.023 (95% CI: 0.003; 0.170) in the study group receiving natalizumab subcutaneously and 0.073 (95% CI: 0.024; 0.220) in the control group. The difference between the groups was not statistically significant.

- Proportion of patients meeting emergency treatment eligibility criteria for MRI lesions

  The analysis showed no statistically significant differences between the analysed groups in terms of the need for qualification for emergency treatment due to MRI lesions.

  In addition, there were no statistically significant differences between natalizumab administered subcutaneously and intravenously in the risk of needing emergency treatment during the randomised phase of the study, regardless of the cause and reason: relapse, new Gd+ lesions, confirmed disability deterioration.

- Annualised relapse rate

  The annualised relapse rate (unadjusted) was 0.08 in the group treated with natalizumab administered subcutaneously, while in the group treated with natalizumab administered intravenously – 0.07. Due to the lack of data on scatter measures for the reported ARR values presented in the reference publications, it was not possible to carry out the statistical analysis of the aforementioned results.

- Relapse

  In the 60th week of the study, the proportion of patients with protocol-defined relapse was 9.1% in the study group and 7.8% in the control group.

  In terms of the risk of relapse, there was no statistically significant difference between treatment with natalizumab administered subcutaneously and with natalizumab administered as an intravenous infusion, over a follow-up period of 60 weeks.

- Disability deterioration

  The degree of disability in the study was assessed using *the Expanded Disability Status Scale* (EDSS).

  Deterioration of disability in the 60th week of the study was confirmed in 4.8% of

the patients in the study group and 5.9% of patients in the control group.

There was no statistically significant difference between natalizumab treatment administered subcutaneously and natalizumab treatment administered intravenously in terms of the risk of confirmed disability deterioration over a follow-up period of 60 weeks.

The mean change in EDSS scores assessing disability severity in the 60th week of the study compared to initial values was -0.04 and -0.16 in the study and control groups, respectively.

Due to the lack of data on scatter measures for the reported values of change from baseline, it was impossible to estimate the difference in mean changes between the groups.

In addition, the results of the pharmacokinetic and pharmacodynamic profile analysis were presented. For the assessment of the pharmacokinetic profile, serum natalizumab concentrations were determined, while for the assessment of the pharmacodynamic profile, integrin α4 receptor saturation was analysed.

In patients taking natalizumab subcutaneously at a dose of 300 mg every 4 weeks and in patients treated with natalizumab administered intravenously at 300 mg every 4 weeks, serum drug concentrations were comparable to initial values throughout the randomised study phase with mean values ranging from 31.0 to 43.7 μg/ml (no differences in minimum serum concentrations were observed between the groups). At the start of the study, mean levels of integrin α4 saturation before drug administration were 78.2-81.8% in all groups. Mean minimum α4-integrin saturation levels remained similar to baseline throughout the randomisation period in arms taking natalizumab every 4 weeks, with values ranging from 76.8% to 83.1% (no significant differences between natalizumab SC and natalizumab IV). Median CD49d expression was comparable to initial values in the study and control groups.

Population of patients previously untreated with natalizumab (DELIVER study)

Efficacy was evaluated for the following endpoints:

- Degree of disability

  The degree of disability in the DELIVER study was assessed using the EDSS (*Expanded Disability Status Scale*) and the MSCF *Multiple Sclerosis Functional Composite*).

  According to the results of the study, the degree of disability and functional status assessed by the EDSS and MSFC, respectively, remained stable in both groups between the first visit and the 32nd week of the study.

  The analysis showed that there were no statistically significant differences between the analysed groups in terms of the functional status of the patients, assessed using the MSFC after 32 weeks of the study.

  However, there was a statistically significantly ($p<0.05$) higher degree of disability for the natalizumab IV group compared to the natalizumab SC group over a follow-up period of 32 weeks according to the EDSS. The observed difference is not due to disability progression but to a reduction in the EDSS score in the natalizumab SC group; moreover, patients in the natalizumab IV group already clinically demonstrated a numerically higher degree of disability at the start of the study than in the group taking natalizumab subcutaneously. Taking into account the change in the EDSS score in relation to initial values, there were no statistically significant differences between the analysed groups in terms of the degree of disability in the EDSS during the follow-up period of 32 weeks.

- Annualised relapse rate

  The unadjusted annualised relapse rate in the analysed groups after 32 weeks of therapy was low at 0.38 for patients treated with natalizumab SC and 0.00 for patients treated with natalizumab IV.

- Assessment of cognitive function, visual impairment and general well-being

The analysis showed that after 32 weeks of the study, the use of natalizumab SC in RRMS patients compared to natalizumab IV was associated with no statistically significant differences in: cognitive function as assessed by the SDMT, visual impairment as assessed by the VFT, general well-being of patients (VAS assessment).

- MRI lesions

  The analysis showed that there were no statistically significant differences between the analysed groups in terms of the change in the number of new or enlarging lesions in the T2 image after 32 weeks compared to initial values. It should be noted that in none of the analysed groups, after starting natalizumab treatment, new lesions on MRI after Gadolinium enhancement were found during the follow-up period of 32 weeks.

In addition, the results of the pharmacokinetic and pharmacodynamic profile analysis were presented. When natalizumab (single dose of drug) was administered by intravenous infusion, serum concentrations of natalizumab showed a typical biphasic time-dependent concentration profile with a rapid distribution phase and a slow elimination phase. In contrast, when administered subcutaneously, natalizumab was slowly absorbed into the systemic circulation, where the time to peak concentration ranged from approximately 2 to 15 days. The analysis of the profiles of mean serum concentrations after the first dose of natalizumab suggests that the elimination phase is comparable between intravenous and subcutaneous administration of the intervention analysed. The bioavailability of natalizumab SC averaged 57.1%, while the bioavailability of intravenous infusions was 100%. The half-life of natalizumab was similar for both forms of drug administration. The mean exposure ($AUC_{0-\infty}$) for natalizumab administered subcutaneously (19.3 mg x hr/mL) was 57% of that observed for intravenous administration (33.8 mg x hr/mL).

The analysis of pharmacodynamic profiles of natalizumab administered subcutaneously and intravenously showed comparable results for most of the analysed parameters. The integrin α4 receptor saturated rapidly (more than 80% of cases – 4 hours after dosing). Similar changes were also observed in the lymphocyte count between the interventions analysed. After the first dose of natalizumab, the lymphocyte count increased, peaking during the first two weeks after the drug was administered. In contrast, mean serum sVCAM concentrations decreased relative to pre-treatment levels, reaching their lowest levels approximately 2 weeks after drug administration.

Safety

Population of patients previously treated with natalizumab (REFINE study)

The safety profile analysis was performed for a safety population including patients who received at least 1 dose of the drug and had at least 1 safety parameter score after starting the treatment.

The analysis showed no statistically significant differences between natalizumab SC and natalizumab IV over a follow-up period of 60 weeks in terms of risk of occurrence:

- total adverse events,
- total adverse events (excluding serious adverse events),
- moderate to serious adverse events,
- serious adverse events,
- severe adverse events,
- treatment-related adverse events,
- adverse events leading to withdrawal from the study,
- adverse events leading to treatment discontinuation

No cases of death were reported in the study group and in the control group.

One patient treated with natalizumab administered intravenously at a dose of 300 mg every 4 weeks was reported to have progressive multifocal leukoencephalopathy (Peto OR=0.15 [95% CI: 0.003;

8.19]); this patient received a total of 34 natalizumab infusions and was positive for anti-JCV antibodies and received immunosuppressive therapy before starting natalizumab treatment. PML cases were considered to be related to the received therapy; after immune reconstitution, they subsided 145 days after symptom onset.

The analysis showed no statistically significant differences between natalizumab SC and natalizumab IV in terms of the risk of individual adverse events during the 60-week follow-up period, except for a statistically significantly ($p<0.05$) higher risk of general disorders and injection site conditions [information protected as a trade secret] when treated with natalizumab S.C. compared to natalizumab IV).

There were no cases of generalised pruritus, rash, generalised rash, maculopapular rash, erythema or haematoma at the injection site in either the study or control group.

Treatment-related adverse effects were observed in 44.4% of patients in the study group and in 29.6% of patients in the control group.

There were no statistically significant differences between the groups receiving natalizumab subcutaneously and intravenously in the risk of treatment-related adverse events such as joint pain, fatigue, headache, injection site pain, nasopharyngitis, urinary tract infections over the 60 weeks of treatment.

However, there was a statistically significantly ($p<0.05$) higher risk of relapse in the natalizumab SC group compared with the natalizumab IV group (OR=9.67 [1.31; 71.41]). The NNH parameter was 11, which means that one out of 11 patients treated with natalizumab SC instead of natalizumab IV will experience a relapse within 60 weeks of the treatment. However, no precise definition was given of what qualified as a relapse in the safety assessment; according to the applicant, these could presumably be events that did not meet the criteria defined for relapse in the study protocol adopted for efficacy assessment.

The analysis showed that there were no statistically significant differences between natalizumab SC and natalizumab IV in terms of the risk of all demonstrated individual serious adverse events over a follow-up period of 60 weeks.

Both in the group of patients treated with natalizumab administered subcutaneously and patients treated with natalizumab administered intravenously, no symptoms of drug immunogenicity were reported. During the randomised treatment phase, all patients tested negative for antibodies directed against natalizumab.

<u>Population of patients previously untreated with natalizumab (DELIVER study)</u>

As concluded by the authors of the publication, no significant differences were observed between the groups analysed in terms of the incidence or nature of general adverse events, injection site reactions, hypersensitivity reactions or anti-natalizumab antibodies. There were no serious adverse events in either group analysed, including treatment-related serious adverse events.

[information protected as a trade secret]

Information based on SmPC

The observed safety profile of natalizumab administered subcutaneously was consistent with the known safety profile of natalizumab administered intravenously, except for injection site pain. For participants taking natalizumab subcutaneously 300 mg every 4 weeks, the overall incidence of injection site pain was 4% (3/71), corresponding to the "frequent" category.

In placebo-controlled studies involving 1,617 patients with multiple sclerosis treated with natalizumab (intravenously) for up to 2 years (placebo: 1,135), adverse reactions leading to treatment discontinuation occurred in 5.8% of patients treated with natalizumab (placebo: 4.8%).

Over the 2-year study period, adverse events were reported by 43.5% of the patients treated with natalizumab (placebo: 39.6%).

In clinical studies involving 6,786 patients treated with natalizumab (administered intravenously and

subcutaneously), the most common adverse reactions associated with natalizumab were headache (32%), nasopharyngitis (27%), fatigue (23%), urinary tract infection (16%), nausea (15%), joint pain (14%) and dizziness (11%).

Information based on safety communications regarding Tysabri *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)*

The FDA has published the "Communication on the risk of PML with the use of natalizumab" [FDA 2018]. In February 2012, the FDA issued a communication that a positive JC virus (JCV) antibody test had been identified as a risk factor for progressive multifocal leukoencephalopathy (PML). The risks and benefits of continued treatment with Tysabri should be carefully considered for patients with anti-JCV antibodies and at least one other known risk factor for PML. The estimated risk of PML in patients with all the three known risk factors is 11/1,000 patients treated with natalizumab. The communication presented here updates the communications previously published by the FDA on the risk of PML associated with the use of Tysabri – on 5 February 2010 and 22 April 2011.

In addition, information presented as part of a drug safety report collected in the FDA Adverse Event Reporting System (FAERS) between April and June 2020 was found on the FDA website. A report of neonatal thrombocytopenia was registered for natalizumab.

However, please note that the above information relates to the intravenous form as the subcutaneous form is not registered in the FDA.

Limitations

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

- The proposed drug programme concerns the population aged 12 and above, whereas the REFINE and DELIVER studies cover the adult patient population. Therefore, it is not possible to determine the efficacy of the assessed technology in the population of patients aged 12-17.
- Patient inclusion in the REFINE and DELIVER studies and eligibility criteria for the B.46 drug programme are not fully consistent.
- The treatment and follow-up period in the DELIVER study was relatively short (32 weeks). Moreover, when interpreting the results of the study, a very small size of the analysed groups of patients and the differences between patients both within and between the analysed groups should be considered. The study did not provide information on the approach used to test the hypothesis: *superiority* or *non-inferiority*. The study was not designed to demonstrate differences between the groups analysed.
- The DELIVER and REFINE studies were the only sources of data available for the intervention evaluated in the decision-making problem under consideration.
- No studies evaluating the effectiveness of the proposed health technology have been found.

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) 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.

The clinical analysis does not include randomised clinical trials proving the superiority of the

technology covered in this recommendation over the comparators so, in the Agency's opinion, the circumstances referred to in Art. 13 of the Act on Reimbursement do arise.

As part of the cost-minimisation analysis, the applicant has not carried out a CER calculation and, at the same time, has not estimated the price at which the cost of applying the proposed technology is equal to the cost of applying the reimbursable comparator with the lowest CER. The applicant stressed that due to the same health outcomes in the DELIVER and REFINE randomised clinical trials, no incremental cost-utility analysis was performed.

The official selling price of the technology in question at which the cost of applying that technology is not higher than the cost of applying the optional technology is [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.

In Poland, the assessment of the cost-effectiveness of natalizumab (Tysabri) administered *subcutaneously* (SC) was performed using a cost-minimisation analysis (CMA).

Assumptions of the analysis:

- comparators: natalizumab (Tysabri) administered intravenously, IV;
- public payer perspective (NHF) and joint perspective (NHF and the patient). The results from both perspectives were assumed to be the same;
- time horizon: 1 year (approximately 13,045 28-day administration cycles of the compared drugs).
- costs included: drugs and administration of drugs.

According to the applicant's estimates, the use of natalizumab administered subcutaneously instead of natalizumab administered intravenously is [information protected as a trade secret] from the public payer perspective. The results from the joint perspective are the same.

The applicant conducted a univariate and multivariate (including outliers) sensitivity analysis that examined the impact of alternative values for the length of the time horizon, the rates of administration of natalizumab IV intravenously and natalizumab SC subcutaneously in the outpatient setting and the cost of natalizumab IV administration.

[information protected as a trade secret] The parameters at which the greatest decrease in the score

compared to baseline was observed were:

[information protected as a trade secret]

The parameters at which the greatest increase in the score compared to baseline was observed were: [information protected as a trade secret]

[information protected as a trade secret]

Limitations

The limitations of the clinical analysis result in the uncertainty of the conclusions based on the economic analysis, in particular of the assumptions on the choice of the analytical method and the financing of the technology in question. The identified studies did not assess the beneficial consequences associated with the type of administration of natalizumab SC vs IV.

In addition, there are no data for Poland – no observational studies are available presenting the costs of care and costs of administration of the analysed drugs among Polish patients.

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

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 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.

The budget impact analysis (BIA) was performed to estimate the public payer's expenditure in case of a positive decision on public financing of the medicinal product Tysabri (natalizumab administered subcutaneously) in the treatment of relapsing-remitting multiple sclerosis [information protected as a trade secret]

Assumptions of the analysis:

- public payer (NHF) perspective;
- time horizon: 2 years (2022-2023);
- costs taken into account: analogous to those in the economic analysis;
- population size - [information protected as a trade secret] patients in the first year and [information protected as a trade secret] patients in the second year of analysis.

According to the results of the basic analysis, the issuance of a positive decision with regards to financing the Tysabri SC medical product from public funds will cause [information protected as a trade secret] of the public payer expenditure [information protected as a trade secret]

The applicant conducted sensitivity analysis for the parameters subject to uncertainty and the main inputs to the model, which included the analysis of 36 alternative scenarios with and without the RSS.

Population size parameters had the greatest impact on the results of the analysis, [information protected as a trade secret]

Only in [information protected as a trade secret] sensitivity analysis scenarios assuming the same administration costs of both forms of the drug, the budget impact was neutral (incremental result equal to PLN 0), in other options considered, there was no change in the conclusion from the basic analysis [information protected as a trade secret]

Limitations

The main limitations of the analysis include the following

- The budget impact was estimated based on sales data, which is a limitation of the analysis. The applicant explains the application of these data by the lack of reliable epidemiological data for the Polish population. In the opinions of clinical experts surveyed by the Agency, in the case of the reimbursement of the drug, the indicated percentage of application of the SC form of the drug among patients treated with natalizumab [information protected as a trade secret]
- In the budget impact analysis, the applicant has taken into account the costs calculated with the model applied in the economic analysis. Therefore, the limitations of economic analysis also apply to budget impact analysis.

[information protected as a trade secret] the main factor affecting the outcome is the cost of administering the drug - natalizumab administered intravenously was assumed to be billed as an "inpatient programme-related admission", which is priced more expensively than the cost assumed for natalizumab administered subcutaneously, where it was assumed to be billed on an outpatient basis ("inpatient programme-related admission"). Thus, [information protected as a trade secret] result from a lower cost of administering natalizumab subcutaneously to the patient. The sensitivity analysis indicates that if the costs of administering both drug forms are equalised, the reimbursement of natalizumab S.C. will have a neutral impact on the budget.

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

[information protected as a trade secret]

Comments on the drug programme

In summary, in the opinion of one of the clinical experts interviewed by the Agency, current trends in the implementation of drug programmes in MS are directed towards the combination of drugs into a single group, and the choice of therapy applied is based on the individual clinical and demographic characteristics of the patient.

It should be noted that the programme stipulates the eligibility of patients from 12 years of age, while Tysabri is registered for use in adult patients. Significantly, in 2015, the Transparency Council issued Position No. 214/2015, in which it recommended the inclusion of the population aged 12 to 18 in the drug programme for natalizumab administered intravenously.

Detailed clinical expert comments are presented in the Agency Verification Analysis.

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 funding indicates an increase in reimbursement costs. [information protected as a trade secret]

Overview of recommendations in relation to the assessed technology

Clinical recommendations

The following clinical recommendations were identified:

- Canadian MS Working Group, 2020 (Canada);
- National Institute for Health and Clinical Excellence, 2019 (Great Britain);
- European Academy of Neurology and European Committee of Treatment of Research in Multiple Sclerosis, 2018 (Europe);
- American Academy of Neurology, 2018 (USA);
- Polish Neurological Society, 2016 (Poland);
- Association of British Neurologists, 2015 (Great Britain).

In summary, all guidelines that have been found indicate the possibility of using natalizumab in the proposed indication, but none of the documents refer to the use of natalizumab administered subcutaneously – only the active substance is indicated.

A detailed description of the individual recommendations can be found in the Agency Verification Analysis

Reimbursement recommendations

The search did not find any recommendations for Tysabri (natalizumab)
in the form for SC administration. The website of the Canadian agency CADTH is the only one that states the pendency of the process relating to the application for funding SC-administered Tysabri under similar terms as IV-administered Tysabri in patients with relapsing-remitting MS (CADTH 2021).

Legal basis for the recommendation

The recommendation was prepared based on the order of 20 July 2021 of the Minister of Health (ref. no: PLR.4500.1319.2021.10.RBO) on the preparation of the President's recommendation on the assessment of Tysabri (natalizumab), solution for injection, 150 mg, 2, pre-filled syringe containing 1 ml of solution, GTIN code: 05713219560252, in the indication: under the drug programme "B.46. Treatment of multiple sclerosis [information protected as a trade secret] or primary progressive multiple sclerosis (ICD-10 G 35)" 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), having obtained Position of the Transparency Council No. 123/2021 of 8 November 2021 on the assessment of Tysabri (natalizumab) under the drug programme "Treatment of multiple sclerosis [information protected as a trade secret] or primary progressive multiple sclerosis (ICD-10 G35)".

References

1. Position of the Transparency Council No. 123/2021 of 8 November 2021 on the assessment of Tysabri (natalizumab) under the drug programme "Treatment of multiple sclerosis after failure of therapy with first-line drugs or rapidly developing severe multiple sclerosis or primary progressive multiple sclerosis (ICD-10 G35)".
2. Verification Analysis No. OT.4231.41.2021 Application for the reimbursement of Tysabri (natalizumab) in the indication: under the drug programme "Treatment of multiple sclerosis [information protected as a trade secret] or primary progressive multiple sclerosis (ICD-10 G 35)". Completion date: 28 October 2021.