Recommendation No. 142/2021
of 23 December 2021
of the President of the Agency for Health Technology Assessment and Tariff System
on the assessment of Entyvio (vedolizumab) under the drug programme "Treatment of Crohn's disease (ICD-10 K50)"

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

- Entyvio (vedolizumab), solution for injection, 108 mg, 2, injection, GTIN code: 07038319122857

in the indication under the drug programme "Treatment of Crohn's disease (ICD-10 K50)", in the existing limit group and dispensing it free of charge **provided that** the costs of vedolizumab s.c. therapy are reduced at least to the costs of vedolizumab i.v. therapy due to the lack of advantages of the technology over the comparator and the limitations of the conducted analyses.

Grounds for the recommendation

Entyvio (vedolizumab) is currently financed under the B.32 drug programme for intravenous administration (IV). The assessed application relates to vedolizumab for subcutaneous administration (SC), which is to be another option for the treatment of Crohn's disease.

As part of the clinical analysis, the results of studies comparing vedolizumab SC to vedolizumab IV were not presented. Therefore, the applicant made an indirect comparison of the above-mentioned medicinal products based on available RCTs (VISIBLE II, GEMINI II). It should also be noted that the proposed drug programme concerns severe Crohn's disease, whereas the studies included in the analysis cover patients with moderate to severe Crohn's disease.

The comparator choice is not questioned. This will probably be the most commonly substituted therapy. However, it cannot be excluded that in practice, other intravenous therapies will also be replaced by vedolizumab administered subcutaneously. Therefore, it is reasonable to reduce the costs of the therapy to reach the costs of cheaper therapies used under the drug programme.

To sum up, the results of the indirect comparison prove that there are no statistically significant differences between vedolizumab SC and vedolizumab IV regarding the following endpoints: clinical remission, increased clinical response, clinical remission with no need to use corticosteroids.

The safety profile of vedolizumab in both forms, which was assessed based on the indirect comparison of the results of the above-mentioned studies, was similar, with the differences not being statistically significant in terms of the frequency of overall serious adverse events, overall adverse events, overall treatment-related adverse events, adverse events leading to treatment discontinuation.

According to the results of the economic analysis, both from the public payer perspective and the joint perspective, the use of vedolizumab SC instead of vedolizumab IV [information protected as a trade secret] in the population, if standard treatment failed, while, in the population after the failure of treatment under the drug programme [information protected as a trade secret]. The uncertainty of drawing conclusions based on the economic analysis concerns, in particular, the fact that the health outcomes were extrapolated over a long period, which was longer than the period considered during the clinical studies. Moreover, due to the assumption made by the applicant that patients would administer vedolizumab SC themselves, during the performance of sensitivity analysis, the scenario in which outpatient visits were more frequent was not considered, e.g. visits considered necessary by the physician at the initial stage of treatment to control the correctness of drug application.

The applicant's budget impact analysis revealed, in the probable variant, [information protected as a trade secret] the public payer expenditure [information protected as a trade secret] However, the main limitation of the analysis is the applicant's assumption related to estimating the target population. There is no information on the number of patients after treatment with vedolizumab IV under the drug programme who could potentially require vedolizumab treatment again over the time horizon assumed in the analysis.

Four positive (CADTH 2021, HAS 2020, PBAC 2020 and SMC 2020) and one negative (second-line treatment: HAS 2020) reimbursement recommendations for the use of the technology (subcutaneous vedolizumab) were identified. Regarding the negative recommendation, the insufficient amount of data proving the efficacy of the proposed treatment in a subpopulation of patients previously untreated with an TNF-alpha inhibitor was stressed.

Therefore, taking into account the position of the Transparency Council regarding the indication specified in the B.32 drug programme "Treatment of Crohn's disease (ICD-10 K50)", it is considered justified to finance the assessed therapy from public funds only if the costs of vedolizumab s.c. therapy are reduced to at least the costs of vedolizumab i.v. due to the lack of advantages of the proposed technology over the comparator and due to limitations of the performed analyses.

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of financing the following medicinal product from public funds:

- Entyvio (vedolizumab), solution for injection, 108 mg, 2, injection, GTIN code: 07038319122857, proposed net sales price is: [information protected as a trade secret]

in the indication, under the B.32 drug programme "Treatment of Crohn's disease (ICD-10 K50)".

Proposed payment and dispensing category: patient - free of charge, under the drug programme, in the existing limit group 1176.0 vedolizumab. The applicant has submitted a proposal for a risk-sharing scheme.

Health problem

Crohn's disease (ICD-10 code: K50) is a full-thickness, mostly granulomatous inflammation that can affect any part of the gastrointestinal tract – from the mouth to the anus. Segmental inflammation with some healthy segments in between is typical. The aetiology is unknown; however, it is most probable that the gut microbiota modified by environmental factors, including diet, plays an important role. The inflammatory process begins in the mucosa and gradually covers all layers of the

gastrointestinal wall, leading to its destruction and fibrosis, as well as the formation of fistulas and strictures.

Epidemiological data on the worldwide incidence of Crohn's disease vary. The incidence of Crohn's disease in Western European and North American countries is estimated at 5 cases per 100,000 inhabitants per year, while the prevalence is estimated at 40-50 cases per 100,000 inhabitants. There is similar incidence and prevalence among men and women.

The disease is chronic and lasts many years – there are usually periods of exacerbation and remission but the symptoms often stay permanently and cause significant disability and the need for surgery due to complications (within 20 years of the disease, almost 50% of patients develop intestinal complications, often changes in the ileum, ileocecal area or in the proximal part of the gastrointestinal tract).

Alternative health technology

Considering the technologies currently financed from public funds, intravenous vedolizumab therapy was adopted as a comparator for the proposed technology.

The choice of the comparator is not questioned. This will probably be substituted therapy. However, it cannot be excluded that in practice, eventually, other intravenous therapies will also be replaced by vedolizumab administered subcutaneously.

Description of the proposed intervention

Vedolizumab is a humanised monoclonal antibody that is an enteric-selective biological immunosuppressive product. The molecule binds specifically to integrin α4β7, which is preferentially expressed on helper T cells captured in the intestines. By binding to α4β7 on the respective lymphocytes, vedolizumab inhibits their adhesion to the mucosal addressin cell adhesion molecule-1 (MAdCAM-1) but not to the vascular cell adhesion molecule-1 (VCAM-1). MAdCAM-1 is expressed mainly on vascular endothelial cells of the intestine and plays an essential role in the retention of T lymphocytes within the gastrointestinal mucosa. Vedolizumab does not bind to or inhibit α4β1 and αEβ7 integrins.

According to the Summary of Product Characteristics (SmPC), Entyvio (vedolizumab) is recommended for the treatment of adult patients with:

- moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.
- moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

The reimbursement indication for Entyvio (vedolizumab) includes patients [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.

A systematic review did not reveal studies that directly compare subcutaneous vedolizumab (WED SC) with intravenous vedolizumab (WED IV). An indirect comparison of WED SC against WED IV, the comparator, was performed based on the results obtained in two studies:

- VISIBLE II (Vermeire 2021, EMA 2020 document, data from clinicaltrials.com (NCT02611817), VISIBLE protocol) - randomised multicentre (194 centres), international study comparing the efficacy and safety of WED SC and placebo (PLC). The subject of this analysis was maintenance (blinded) treatment and the total number of patients was N=409 (WED SC n=275; PLC n=134). Follow-up period: 52 weeks.
- GEMINI II (Sandborn 2013, Sands 2017, document EMA 2014) - randomised, multicentre (285 centres), international study comparing the efficacy and safety of WED IV and PLC. The subject of the analysis was maintenance (double-blinded) treatment and the total number of patients was N=308 (WED IV n=154; PLC n=153). Follow-up period: 52 weeks.

The risk-of-bias assessment according to Cochrane Collaboration for the VISIBLE II and GEMINI II studies for all analysed domains was determined as low.

Efficacy

Indirect comparison based on VISIBLE II (WED SC vs PLC) and GEMINI II (WED IV vs PLC) studies

Efficacy was assessed for the following endpoints: clinical remission, increased clinical response, clinical remission with no need to use corticosteroids. In the case of all above-mentioned endpoints, for the follow-up period of 52 weeks, there was no statistically significant difference between WED SC and WED IV both in the general population and in the population of patients previously untreated with TNF-alpha inhibitors and after failure of treatment with TNF-alpha inhibitors.

Comparison of WED SC and PLC - VISIBLE II study

Efficacy was assessed for the full analysis set (FAS), taking into account all patients included in the VISIBLE II study, i.e. patients who responded to vedolizumab IV administered during the induction phase and received vedolizumab SC as maintenance therapy.

In the subcutaneous vedolizumab group, changes in the following endpoints were reported more frequently than in the placebo group:

- Clinical remission - 48% vs 34.3%, RD=0.137 (95% CI: 0.038; 0.237; p=0.008). The difference was statistically significant.
- Clinical response - 52.0% vs 44.8%; RD=0.073 (95% CI: -0.030; 0.175; p=0.167). The difference was not statistically insignificant.
- Clinical remission with no need to use corticosteroids - 45.3% vs 18.2%, RD=0.271 (95% CI: 0.119; 0.423; p=0.002). According to the information provided by the authors of the study, statistical significance cannot be determined due to the lack of significance for increased clinical response.
- Sustained clinical remission - 28% vs 22.4%, RD=0.056 (95% CI: -0.027; 0.139). The difference was statistically significant.
- Faecal calprotectin levels ≤250 μg/g - 60.5% vs 31.7%, RD=0.29 (95% CI: 0.15; 0.43). The difference was statistically significant.
- Quality of life - the VISIBLE II study assessed health-related quality of life (HRQoL) with the use of four questionnaires: IBDQ, EQ-5D (including EQ-5D VAS) and WPAI-CD. The change recorded in

both WED SC and PLC between week 0 and week 52 was clinically significant in favour of the proposed technology.

Safety

Indirect comparison based on VISIBLE II (WED SC vs PLC) and GEMINI II (WED IV vs PLC) studies

There were no statistically significant differences between WED SC and WED IV regarding the frequency of overall treatment-related adverse events and adverse events leading to treatment discontinuation.

As far as the VISIBLE II study is concerned, no deaths were reported during treatment with vedolizumab SC or among patients taking placebo during the follow-up period of 52 weeks. As far as the GEMINI II study is concerned, one death was reported for patients using WED IV, while no deaths were reported in the control group.

Direct comparison of WED SC and PLC - VISIBLE II study

The analysis conducted to compare WED SC and PLC during the follow-up period of 52 weeks showed statistically significant differences only in the case of adverse events by system organ class (SOC) related to urinary tract infections, which occurred more often in the PLC group than in the WED SC group (4.5% vs 0.4%).

There were no statistically significant differences between WED SC and PLC regarding the endpoints: overall safety profile, serious adverse events by system organ class (SOC), adverse events by system organ class (SOC).

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

Information based on SmPC

According to the SmPC for Entyvio, very common adverse effects include nasopharyngitis, headache and joint pain.

Information based on safety communications regarding Entyvio *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)*

According to the Pharmacovigilance Risk Assessment Committee (PRAC) 2020 document, there is currently insufficient evidence proving a correlation between vedolizumab treatment and the development of Evans syndrome, autoimmune haemolytic anaemia or immune thrombocytopenic purpura.

In a document from 2019 found on the FDA website, it is stated that the use of vedolizumab may be associated with a risk of the occurrence of the following adverse effects: infusion-related and hypersensitivity reactions, infections, progressive multifocal leukoencephalopathy and liver damage. Furthermore, an FDA communication of 2020 on Entyvio regarding pancreatitis was identified, in which the FDA assessed the need for regulatory action.

The applicant reported adverse events in patients treated with WED based on the European database of suspected adverse drug reaction reports (ADRReports). The most common adverse events included general injection site disorders and conditions, gastrointestinal disorders, parasitic infections and nervous system disorders (as at 29 May 2021). Moreover, a more recent ADR report was found, according to which the most common adverse events included general injection site disorders and conditions, gastrointestinal disorders, trauma, poisoning, complications after surgery, musculoskeletal and connective tissue disorders, nervous system disorders and skin and subcutaneous tissue disorders (as at 4 December 2021).

Information on possible adverse effects related to Entyvio (vedolizumab) was found on the website of the World Health Organisation Monitoring Centre. The most common adverse events were general injection site disorders and conditions, gastrointestinal disorders, trauma, poisoning, complications after surgery and parasitic infections.

Limitations

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

- No studies directly comparing the efficacy and safety of WED SC and WED IV in the target population. Therefore, an indirect comparison was performed, which is characterised by limitations.
- The inclusion criteria for the VISIBLE II study cover patients with moderate or severe Crohn's disease, while the proposed drug programme applies only to patients with severe Crohn's disease.
- No studies on the effectiveness and safety of the proposed solution were found. It should be noted that the use of subcutaneous WED is a relatively recent therapy.

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

Proposed risk-sharing scheme [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 cost-effectiveness of the therapy with subcutaneous (SC) vedolizumab (Entyvio) in Poland was assessed with the use of cost-minimisation analysis (CMA). For the analysis, the following were assumed:

- comparators: intravenous (IV) vedolizumab (Entyvio);
- public payer perspective (National Health Fund, NHF) and joint perspective (NHF and patient). The results regarding both perspectives are similar;
- time horizon: lifetime (64 years);
- similar efficacy of the assessed treatments was assumed, categories of differential costs were

the only ones considered;

- self-administration of vedolizumab SC by a patient was assumed, and the drug was dispensed once every 24 weeks.

As estimated by the applicant, in the population of patients after the failure of standard treatment, the use of vedolizumab SC instead of vedolizumab IV [information protected as a trade secret] from the public payer perspective.

In the population of patients after the failure of treatment under the drug programme (after failure of treatment with TNF-alpha inhibitors), the use of vedolizumab SC instead of vedolizumab IV [information protected as a trade secret]

from the public payer perspective.

The applicant performed a one-way sensitivity analysis for the key parameters that are characterised with the greatest uncertainty and potentially the greatest impact on results.

The sensitivity analysis performed in the population of patients after the failure of standard therapy, considering the RSS, showed that drawing conclusions [information protected as a trade secret]

Results of the sensitivity analysis conducted in the population of patients after the failure of treatment under the drug programme – both with and without the RSS – [information protected as a trade secret]

Limitations

The uncertainty of drawing conclusions based on the economic analysis concerns, in particular, the fact that the health outcomes were extrapolated over a long period, which was longer than the period considered during the clinical studies. Furthermore, the applicant, in their analyses, did not make estimates for the entire assessed population, i.e. including both patients after the failure of standard treatment and patients after the failure of treatment under the drug programme. Moreover, due to the assumption made by the applicant that patients would administer vedolizumab SC themselves, during the performance of sensitivity analysis, the scenario in which outpatient visits were more frequent was not considered, e.g. visits considered necessary by the physician at the initial stage of treatment to control the correctness of drug application.

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.

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 Reimbursement Act do arise.

The official selling price (OSP) at which the cost of using the proposed technology is not higher than the cost of using the optional technology is:

- in the population of patients after the failure of standard treatment [information protected as a trade secret]

- in the population of patients after the failure of treatment under the drug programme [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.

The budget impact analysis was performed to estimate the expenditure of the public payer in case of a positive decision on the public financing of Entyvio (vedolizumab administered subcutaneously) to treat adult patients with Crohn's disease, according to the provisions of the draft B.32 drug programme.

Assumptions of the analysis:

- the perspective of the entity obliged to finance the interventions from public funds (public payer, NHF) and also the joint perspective: NHF and patient.
- time horizon: 2 years (from March 2022 until the end of February 2024);
- included costs: cost categories taken from economic analysis;
- population size:
  - in the 1st year [information protected as a trade secret] patients,

  in the 2nd year [information protected as a trade secret] patients.

According to the results of the basic analysis, the issuance of a positive decision with regards to financing Entyvio SC from public funds would be expected to involve: [information protected as a trade secret]

In the probable variant, the most significant changes in the incremental result as an increase in expenditure compared to the basic variant were observed in the scenarios where: [information protected as a trade secret]

Limitations

The main limitations of the budget impact analysis stem from the uncertainty of the population estimates. There is no information on the number of patients after treatment with WED under the drug programme who could potentially require WED treatment again over the time horizon assumed in the analysis. Furthermore, the limitations identified at the cost modelling stage of the economic analysis also apply to this analysis.

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

Comments on the proposed risk-sharing scheme

Not applicable.

Comments on the drug programme [information protected as a trade secret]

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.

Not applicable.

Overview of recommendations in relation to the assessed technology

Clinical recommendations

Eight clinical guidelines were identified on the websites of the following scientific societies:

- Polish Society of Gastroenterology (PTG-E, Poland),
- European Crohn's and Colitis Organization (ECCO, Europe),
- American Gastroenterological Association (AGA, USA),
- British Society of Gastroenterology (BSG, UK),
- National Institute for Health and Care Excellence (NICE, UK),
- National Health Service (NHS 2021, UK),
- French National Consensus (FNS 2021, France),
- Canadian Association of Gastroenterology, (CAG 2019, Canada).

To sum up, all guidelines refer to the treatment of Crohn's disease with the use of vedolizumab, while the guidelines of two societies – NHS 2021, PTG-E 2021 – refer to vedolizumab administered subcutaneously. The NHS 2021 guidelines report that vedolizumab is recommended as an option for the treatment of moderate to severe Crohn's disease in patients who have had inadequate response to a TNF inhibitor, loss of response or intolerance to a TNF inhibitor. In addition, treatment schemes with subcutaneous vedolizumab are indicated. According to the PTG-E 2021 guidelines, the risk of severe infections is significantly lower in the case of vedolizumab treatment compared to treatment with TNF inhibitors. Vedolizumab is the preferred therapeutic option for patients with inflammatory lesions located in the large intestine, especially in the population of elderly patients and patients with comorbidities. According to these guidelines, the efficacy of vedolizumab has been confirmed in both remission induction and maintenance. The guidelines indicate the possibility of changing the route of administration of vedolizumab – from intravenous to subcutaneous.

Reimbursement recommendations

Five reimbursement recommendations for Entyvio (vedolizumab) administered subcutaneously in the treatment of Crohn's disease were identified – 4 positive (CADTH 2021, HAS 2020, PBAC 2020 and SMC 2020) and 1 negative (HAS 2020). In the case of the positive recommendations, particular

attention is paid to the favourable results of the VISIBLE II study, providing a potentially relevant maintenance therapy option for the patient in the form of subcutaneous administration or enabling treatment of patients who live in areas where access to intravenous treatment is difficult. The negative HAS 2020 recommendation mainly points to the insufficient amount of data proving the efficacy of the proposed treatment in the subpopulation of patients previously untreated with an TNF-alpha inhibitor. [information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared based on the order of the Minister of Health of 13 October 2021 (ref. no.: PLR.4500.1687.2021.16.PTO) concerning the preparation of the President's recommendation on the assessment of: Entyvio (vedolizumab), solution for injection, 108 mg, 2, injection, GTIN code: 07038319122857 in the indication: under the B.32 drug programme "Treatment of Crohn's disease (ICD-10 K50)" 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. 140/2021 of 20 December 2021 on the assessment of Entyvio (vedolizumab) under the drug programme "Treatment of Crohn's disease (ICD-10 K50)"

References

1. Position of the Transparency Council No. 140/2021 of 20 December 2021 on the assessment of Entyvio (vedolizumab) under the drug programme "Treatment of Crohn's disease (ICD-10 K50)"
2. Verification Analysis No. OT.4231.51.2021 Application for the reimbursement of Entyvio (vedolizumab) under the drug programme: "Treatment of Crohn's disease (ICD- 10 K50)". Completion date: 9 December 2021