Recommendation No. 127/2021
of 25 November 2021
of the President of the Agency for Health Technology Assessment and Tariff System
on the assessment of Mavenclad (cladribine) under the drug programme [information protected as a trade secret]

The President of the Agency recommends the reimbursement of Mavenclad, Cladribinum, Tablets, 10 mg, 1 tablet, GTIN code: 04054839365331; Mavenclad, Cladribinum, Tablets, 10 mg, 4 tablets, GTIN code: 04054839365348 and Mavenclad, Cladribinum, Tablets, 10 mg, 6 tablets, GTIN code: 04054839365355 under the drug programme [information protected as a trade secret] with the payment level for the patient - free of charge, within the existing limit group "1200.0, cladribine" provided that the costs of the assessed technology are equal to the costs of reimbursed therapies in this indication.

Grounds for the recommendation

Taking into account the position of the Transparency Council, available scientific evidence, clinical guidelines and reimbursement recommendations, the President of the Agency considers the reimbursement of Mavenclad provided that the costs of the assessed technology are equal to the costs of other reimbursed therapies in this indication.

Mavenclad is currently funded for the treatment of multiple sclerosis (MS) under the B.46 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)". The application in question relates to the extension of the availability of oral cladribine (CLA) for patients at an earlier disease stage, under the drug programme [information protected as a trade secret].

The clinical analysis did not present the results of studies in which the efficacy of CLA was directly compared with other drugs currently available in the drug programme [information protected as a trade secret]. According to clinical recommendations, the main aim of multiple sclerosis treatment is to prevent disability progression. In view of the above, the applicant's clinical analysis for the occurrence of 3-month confirmed disability progression (3mCDP) for all therapies used in the drug programme, [information protected as a trade secret] for which estimation was possible, suggests treatment equivalence, understood as the absence of a statistically significant difference in an indirect comparison.

There was a statistically significant reduction in ARR vs TER, IFN and GA, IS difference in PK NEDA, which was defined as the absence of clinical and radiological features of MS activity in patients, assessed after a follow-up period of 24 months (vs TER, DF, GA) and IS lower risk of relapse (MS relapse) vs GA, IFN, TER and no IS difference for this endpoint vs DF.

It was also noted that in the 2018 drug assessment, there were many more IS differences compared to comparators for this drug in the indication proposed at that time (e.g. for ARR vs GA, IFN B1a, DMF, TER, 3mCDP vs DF, 6mCDP vs DMF) under the B.46 drug programme "Treatment of multiple sclerosis after the failure of therapy with first-line drugs or rapidly developing severe multiple sclerosis or primary progressive multiple sclerosis (ICD-10 G35)", the conclusions were based on the results in the indication for the HDA population. In the currently assessed application, this range of IS differences was not demonstrated, while the application was based on the results in the indication in the ITT population. This also indicates that it is reasonable to aim for a reduction in the cost of therapy (equal to the cost of other therapies).

At the same time, the safety profile of CLA is comparable to drugs used in the drug programme [information protected as a trade secret] but the use of CLA is associated with an increased risk of lymphopenia.

Efficacy considerations are based on scientific evidence with lower reliability, such as network meta-analysis (NMA). The reliability of the results presented in the clinical NMA was further limited by combining results from studies with inconsistent methodology.

According to the applicant's estimates, the use of CLA instead of drugs from the drug programme is [information protected as a trade secret] from the NHF perspective: [information protected as a trade secret]. The estimated ICUR under the RSS [information protected as a trade secret] cost-effectiveness threshold [information protected as a trade secret] and falls within the scope of [information protected as a trade secret]. The economic analysis lacks the modelling of subsequent lines of treatment. Patients switch to symptomatic treatments after treatment with cladribine or one of the comparators, which does not correspond to the clinical practice of MS treatment. This limitation of the economic analysis certainly increases the uncertainty of the estimates.

The budget impact analysis indicates that under the likely option of market share takeover, public payer expenditure, when the RSS is considered, would increase by [information protected as a trade secret] in the first and by [information protected as a trade secret] in the second year. The main limitation of the budget impact analysis is the uncertainty in estimating the population size.

Cladribine tablets are recommended as a treatment option: in patients with rapidly progressing, severe RRMS and in patients with RRMS after failure of previous treatment (NICE 2021), but are not recommended in active RRMS due to insufficient evidence of efficacy (Prescrire 2018). Reimbursement recommendations are positive, noting the cost-effectiveness of the treatment relative to placebo (NCPE 2018, NICE 2019, PBAC 2018), the efficacy superiority of cladribine tablets compared to placebo (CADTH 2018, NICE 2019, SMC 2018) and similar therapeutic value with fingolimod (ZIN 2018).

Subject of the application

Mavenclad is currently financed for the treatment of multiple sclerosis under the B.46 drug programme "Treatment of multiple sclerosis after the failure of therapy with first-line drugs or rapidly developing severe multiple sclerosis or primary progressive multiple sclerosis (ICD-10 G35)". The application in question concerns the extension of the availability of oral cladribine.

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

- Mavenclad (cladribine), tablets, 10 mg, 1 tablet, GTIN code: 04054839365331; proposed net sales price [information protected as a trade secret];
- Mavenclad (cladribine), tablets, 10 mg, 4 tablets, GTIN code: 04054839365348; proposed net sales price [information protected as a trade secret];
- Mavenclad (cladribine), tablets, 10 mg, 6 tablets, GTIN code: 04054839365355; proposed net sales price [information protected as a trade secret];

under the drug programme [information protected as a trade secret].

Proposed payment and dispensing category: patient payment level - free of charge, in the above indicated drug programme, in the existing limit group "1200.0, cladribine". The applicant has submitted a proposal for a risk-sharing scheme.

Health problem

Multiple sclerosis (MS) is a chronic, demyelinating disease of the central nervous system of unknown aetiology. There are four main forms of the disease: *relapsing-remitting MS* (RRMS), *primary progressive MS* (PPMS), *secondary progressive MS* (SPMS) and *progressive relapsing MS* (PRMS).

The symptoms of MS are varied, with its clinical presentation depending largely on the location of the lesions. The most commonly listed MS symptoms by the Polish Multiple Sclerosis Society (PTSR) include: spasticity, or increased muscle tension (muscle spasms and stiffness, which have a significant impact on the patient's motor impairment); fatigue, or fatigue unpredictable or inadequate to physical effort. The EDSS (Expanded Disability Status Scale) is most commonly used to assess the clinical status of MS patients. Multiple Sclerosis Functional Composite (MSFC) is less commonly used.

McDonald's criteria (2005 and 2010 revisions) are used to diagnose MS. An MS relapse is defined as the occurrence of a new symptom or an exacerbation of an existing symptom, lasting ≥24h, that causes a neurological deterioration by ≥1 EDSS score. The symptom(s) that developed during a relapse may subside completely, but often the improvement is only partial and some degree of neurological loss usually remains. Successive relapses usually lead to increasing disability.

MS is usually diagnosed in people between 20 and 40, but it can occur at younger and older ages as well. Women are diagnosed 2-3 times more often than men. According to the data taken from Narodowy Program Leczenia Chorych ze Stwardnieniem Rozsianym [National Programme for the Treatment of Patients with Multiple Sclerosis] prepared in 2006-2008, the prevalence rate in Poland is approximately 150/100,000 population, while according to the estimates of the Polish Multiple Sclerosis Society, there are approximately 45,000 patients suffering from multiple sclerosis in Poland.

In the natural course of RRMS, symptoms that worsen or occur *de novo* during a relapse may subside completely (without neurological loss) or partially (with neurological loss remaining). Due to the highly variable course of the disease, the prognosis is difficult to determine, but it is known to be best in patients whose initial symptoms were transient and of low severity and whose subsequent symptoms have taken a long time to develop.

Alternative health technology

MS treatment is currently funded in Poland under the B.29 drug programme "Treatment of multiple sclerosis (ICD-10 G35)" and the B.46 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)".

The application concerns the inclusion of cladribine (CLA) treatment in the drug programme [information protected as a trade secret]. The applicant identifies currently funded technologies under the drug programme [information protected as a trade secret] that will potentially be replaced by CLA as alternative ones, i.e.: interferon beta 1a (INF1a), interferon beta 1b (INF1b), peginterferon beta-1a (pINF1a), glatiramer acetate s(GA), dimethyl fumarate (DF), teriflunomide (TER). The choice of comparators is legitimate.

Description of the proposed intervention

Mavenclad contains active substance cladribine, which is a nucleoside analogue of deoxyadenosine. The role of cladribine in the treatment of multiple sclerosis is not clarified.

According to the Summary of Product Characteristics (SmPC), Mavenclad is indicated for use in adults for the treatment of a highly active form of MS, confirmed by clinical symptoms or diagnostic imaging (MRI) findings.

The application relates to the use of Mavenclad under the drug programme [information protected as a trade secret], in which the proposed provisions do not refer to the high disease activity (HDA)

form. Although the criteria for the occurrence of HDA are not clearly defined, it would be reasonable to assume that the proposal is for an indication narrower than that registered.

Proposed risk-sharing scheme

The risk-sharing scheme proposed by the applicant [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 purpose of the applicant's clinical analysis was to assess the efficacy and safety of cladribine tablets at a dose of 3.5 mg/kg (CLA) in the relapsing form of MS, compared with alternative technologies reimbursed under the drug programme [information protected as a trade secret], i.e. INF1a, INF1b, pINF1a, GA, DF and TER.

The CLARITY randomised controlled trial (RCT) was included in the applicant's review of primary studies. The population consisted of adults with RRMS (N = 1,326). CLA was administered in the applied intervention arm (n = 433) and placebo in the control arm (PLC, n = 437). The follow-up period was 96 weeks. Time to confirmed disability progression (CDP) was assessed as well as surrogate endpoints, including the annualised relapse rate (ARR) or changes observed in imaging findings. In addition, results from the CLARITY EXTENSION phase were presented, in which 98 patients receiving CLA (cladribine tablets at a dose of 3.5 mg/kg) during the primary phase of the study received placebo for the next 2 years.

The results of the network meta-analysis (NMA), in which indirect comparisons of CLA with alternative technologies were performed, were also presented. RCTs with DMDs approved by US or European regulatory agencies were included in the analysis. The population consisted of adult patients with RRMS (at least 80% of the population in the RCT). The endpoints assessed included the occurrence of confirmed disability progression (CDP), annualised relapse rate (ARR) and no evidence of disease activity (NEDA).

Efficacy

No studies were found directly comparing CLA with any of the alternative technologies
i.e. INF1a, INF1b, pINF1a, GA, DF and TER.

<u>Direct comparison of CLA vs PLC – RCT CLARITY</u>

After 96 weeks of follow-up, 85% of patients receiving CLA and 75% of the ones receiving PLC were free of 3-month confirmed disability progression (3mCDP).

The time of 3mCDP for the 10th percentile of the population did not exceed 13.6 months in CLA and 10.8 months in PLC. The hazard ratio was HR 0.44 (95%CI 0.34; 0.58) and the result was statistically significant.

Time to first relapse for the 15th percentile of the population did not exceed 13.4 months in CLA and 4.6 months in PLC. The hazard ratio was HR 0.67 (95%CI: 0.48; 0.93) and the result was statistically significant.

The primary endpoint of the study was the annualised relapse rate (ARR). There were 109 relapses in the CLA arm and 256 in the PLC arm. The ARR in the CLA arm was 0.14 relapses/year/person (95%CI:

0.12; 0.17) and in the PLC arm: 0.33 relapses/year/person (95%CI: 0.29; 0.38). The difference was statistically significant.

The results obtained from imaging findings were also assessed. In terms of the comparison of CLA vs PLC, there were: a lower mean number of lesions in T1-weighted Gadolinium-enhanced images (0.12 vs 0.91), a lower mean number of active lesions in T2-weighted images (0.38 vs 1.43) and a lower mean number of combined unique lesions (0.43 vs 1.72). The differences were statistically significant in favour of CLA.

In the extended phase of the study (CLARITY EXTENSION), placebo after CLA was subsequently used in 98 patients, of whom 9 patients experienced discontinuation (including 2 deaths). The ARR of 0.15 relapses/year/person was reported (97.5%CI: 0.09; 0.21). Due to the implementation of a different confidence interval, i.e. 97.5% vs 95% in the main study, a direct comparison of the numerical values of confidence intervals and statistical significance is not valid. 75.6% of patients remained relapse-free after a total of 4 years of follow-up – this result was 4 percentage points lower than that obtained in the population after 2 years of treatment in the main study. The 3mCDP score was not recorded in 72.4% of patients. Considering the results of a long-term follow-up, the effect of CLA achieved after a two-year treatment can be considered to remain relatively stable.

Indirect comparison – network meta-analysis

Forty-four studies assessing 12 disease-modifying drugs (DMD) were included in the network meta-analysis (NMA) performed as part of Siddiqui 2018. The studies were published between 1987 and 2017, and they showed variability in diagnostic criteria, blinding method, study phase, sample size (31 to 2,244), definition of relapse and definition of disability progression.

In patients with active RRMS, the difference for the results for the occurrence of 3mCDP when comparing CLA with other DMDs (except pINF1a – no data) was not statistically significant.

In the active RRMS population, CLA use was associated with a statistically significant ($p < 0.05$) 58% reduction in ARR compared with placebo, which translated into a significant 36-48% reduction in indirect comparison through the placebo arm with TER, IFN, GA. At the same time, the difference in CLA versus DF, using a random effects model, the use of which is appropriate given the methodological and clinical heterogeneity, was not statistically significant.

The NNT median, or number of patients treated to avoid one relapse event compared with placebo over the 2-year period was 3 for cladribine and DF, for all other DMDs it ranged from 5 to 8.

The occurrence of the NEDA endpoint, which was defined as the absence of clinical and radiological features of MS activity in patients, was assessed after 24 months of follow-up. Patients taking CLA were shown to have a significantly increased likelihood of NEDA (i.e. absence of symptoms of disease activity) compared with placebo (OR 4.69), which translated into statistically significant differences when comparing CLA with TER (OR 2.00), DF (OR 2.72) and GA 20 mg (OR 3.39).

The use of CLA is associated with a statistically significantly lower likelihood of relapse, defined as an MS relapse at 1 year, compared with all funded technologies except DF, with which it is comparable. CLA also contributes to a significant increase in the chance of disease inactivity at clinical and MRI assessment after two years in relation to the therapeutic options available for comparison. However, there were no differences in the protection against disability progression as defined by 3-month confirmed disease progression after 24 months following treatment and in the prevalence of total adverse reactions reported by patients.

Safety

Direct comparison of CLA vs PLC – RCT CLARITY

Safety data are presented for 96 weeks of follow-up. There were 2 deaths (0.5%)

in the CLA arm and 2 deaths (0.5%) in the PLC arm.

Adverse events (*AEs*) were observed in 80.7% of patients in the CLA arm and in 73.3% of patients in the PLC arm. AEs leading to treatment discontinuation occurred in 1.2% of patients in the CLA arm

and 1.1% in the PLC arm. Lymphocytopenia was reported more frequently in the CLA arm than the PLC arm (RR 11.76; 95%CI: 5.78, 23.91; p = IS). Severe neutropenia (as assessed by the researchers) was reported in one patient in the CLA group.

The occurrence of cancers (including benign, malignant or unspecified) was reported as serious AEs in 1.4% of CLA patients (3 cases of uterine fibroids cancer, 1 malignant melanoma cancer, 1 ovarian cancer and 1 metastatic pancreatic cancer) compared with none in patients in the PLC group.

In the group of patients qualified for the CLARITY EXTENSION study, 75.5% of patients had AEs; a total of 16.3% of AEs were classified as serious (almost twice as many as in the CLARITY study). The occurrence of the most common AEs (headache, nasopharyngitis, upper respiratory tract infections) remained similar, except that lymphocytopenia was reduced to 9.2%. AEs resulted in treatment discontinuation in 3.1% of patients. Two further cases of malignancy were reported: one case of melanoma and one case of basal cell carcinoma cancers. In the group of patients taking placebo, two further deaths were reported after cladribine: one drowning and one death from unknown causes.

Indirect comparison – network meta-analysis

For safety assessment, 25 studies were considered appropriate for inclusion in the NMA. All AEs reported in each study were analysed. The definition of AE varied across the studies, with the main difference being the cut-off point approach (e.g. >10% of the population) and the inclusion of relapse due to multiple sclerosis as an AE.

The results indicate that there is no statistically significant difference in overall AE risk for CLA compared with placebo and most DMDs. The overall risk of AE with CLA was comparable with other oral DMDs, all IFN-beta regimens and GA 40 mg. There was a numerical but not statistically significant increase in the overall risk of AE after pINF1a treatment.

Additional efficacy and safety analysis

Information based on SmPC

According to the SmPC of Mavenclad, the adverse effects of the greatest clinical relevance reported in multiple sclerosis patients receiving cladribine at the recommended total dose of 3.5 mg/kg for 2 years in clinical studies were lymphopenia and hemiplegia. The incidence of hemiplegia was higher during the period of grade 3 or 4 lymphopenia (<500 to 200 cells/mm³ or <200 cells/mm³) compared to the period when the patients did not have grade 3 or 4 lymphopenia.

The role of cladribine is closely related to a reduction in the number of lymphocytes. The effect on the lymphocyte count is dose-dependent. In clinical studies, reductions in neutrophil, red blood cell, haematocrit, haemoglobin and platelet counts were also observed compared to initial values, although these parameters usually remain within the normal range.

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

No safety communications were found on the URPL, EMA and FDA websites that were not included in the current SmPC.

Limitations

The main limitation of the applicant's clinical analysis, which significantly affects the conclusion, is the lack of results of randomised clinical trials directly comparing the efficacy and safety of CLA against reimbursable alternative technologies, i.e. INF1a, INF1b, pINF1a, GA, DF and TER.

The registration indication is for the HDA population, but not every study presented results for this population. Additionally, there are discrepancies in the studies regarding the definition of HDA. In particular, the HDA population from the CLARITY study was wider than in the other studies.

The studies included in the network meta-analysis were published over 22 years (1995 to 2017), and they differed in terms of methodology (different diagnostic criteria over the years, presence or

absence of blinding across the studies), characteristics of the included population (mean number of relapses in the previous year, duration of the disease, previous treatment - type of therapy or no treatment) and the definition of endpoints. With this in mind, the interpretation of the results of the network meta-analysis should be done with particular caution.

The results of the comparison of the incidence of lymphopenia against reimbursable alternative technologies were not presented in the safety analysis. Lymphopenia was one of the more common adverse events in the CLARITY study and was considered an adverse event of special interest in the CLARITY EXTENSION study.

Other limitations are presented in the Agency Verification Analysis.

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 (3 x PLN 55,586).

The cost-effectiveness ratio does not estimate or determine the value of life, but it only enables its assessment and the use of this assessment to choose the therapy associated with the potential best use of the currently available resources.

The aim of the analysis was to assess the economic viability of the use of Mavenclad (cladribine, CLA) under the drug programme [information protected as a trade secret], in the population of patients for whom, according to the proposed provisions of the drug programme, [information protected as a trade secret]. Cost-utility analysis (CUA) was carried out, in which the use of CLA was compared with drugs available in the drug programme [information protected as a trade secret], i.e. interferon beta-1a (Rebif and Avonex separately), interferon beta-1b, peginterferon beta-1a, dimethyl fumarate, glatiramer acetate and teriflunomide. The analysis was conducted from the public payer perspective (NHF), from the joint perspective (NHF and recipient) and from the social perspective. A time horizon of 50 years was adopted, which was considered to be lifelong. The costs of drugs, diagnostics and monitoring as well as the costs of outpatient visits under the programme, costs of treating adverse events, medical conditions (dependent on the patient's EDSS) and the costs of MS relapses were included in the analysis.

According to the applicant's estimates, the use of CLA instead of drugs from the drug programme [information protected as a trade secret] is [information protected as a trade secret] from the NHF perspective. The estimated ICUR for the CLA comparison against each comparator is:

- Interferon beta-1b: [information protected as a trade secret] with the RSS and PLN 130,003 without the RSS
- Dimethylfumarate: [information protected as a trade secret] with the RSS and PLN 134,233 without the RSS
- Interferon beta-1a (Rebif 44µg): [information protected as a trade secret] with the RSS and PLN 134,993 without the RSS
- Interferon beta-1a (Avonex): [information protected as a trade secret] with the RSS and

PLN 143,184 without the RSS
- Teriflunomide: [information protected as a trade secret] with the RSS and PLN 145,490 without the RSS
- Peginterferon beta-1a: [information protected as a trade secret] with the RSS and PLN 146,016 without the RSS
- Glatiramer acetate: [information protected as a trade secret] with the RSS and PLN 180,506 without the RSS

ICUR values, when the RSS is considered, [information protected as a trade secret]. For ICUR values when the RSS is not considered, the cost-effectiveness threshold is exceeded only for glatiramer acetate.

The applicant's estimate of the threshold net sales price of the drug at which the cost of an additional quality-adjusted life year is equal to the threshold referred to in Art. 12 point 13 and Art. 19 sec. 2 point 7 of the Act, is for glatiramer acetate, [information protected as a trade secret] than the proposed net sales price and shall be respectively [information protected as a trade secret] pack of 1 tablet, [information protected as a trade secret] pack of 4 tablets and [information protected as a trade secret] pack of 6 tablets from the NHF perspective and [information protected as a trade secret] pack of 1 tablet, [information protected as a trade secret] pack of 4 tablets and [information protected as a trade secret] pack of 6 tablets from the joint perspective. For other comparators, the threshold net sales price is [information protected as a trade secret] than the price proposed in both the NHF and the joint perspective.

The applicant provided a deterministic and probabilistic sensitivity analysis. When assuming a 20-year time horizon and disability progression (3mCDP), the ICUR including the RSS compared with [information protected as a trade secret] is [information protected as a trade secret] the cost-effectiveness threshold. Similarly, when assuming minimal cladribine ICUR efficacy with the RSS [information protected as a trade secret]. Cost-utility probabilities including the RSS depending on the comparator is [information protected as a trade secret].

Limitations

The main limitation of the economic analysis is that it is based on estimates of efficacy determined on the basis of the network meta-analysis, the results of which are subject to considerable uncertainty.

The economic analysis lacks the modelling of subsequent lines of treatment. Patients switch to symptomatic treatments after treatment with cladribine or one of the comparators, which does not correspond to the clinical practice of MS treatment.

Other limitations are 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 contain randomised clinical trials directly demonstrating the superiority of the proposed technology over reimbursed comparators, so the circumstances of Art. 13 of the Act on Reimbursement do arise. The estimates provided by the applicant pursuant to Art. 13 were incorrect, as the costs were equalised on the assumption of differences in the efficacy of the therapy, which does not correspond to the provisions of Art. 5 sec. 6 point 1-3 of the Regulation of the Minister of Health of 8 January 2021 on the minimum requirements to be met by analyses included in the applications for including a medical products, a foodstuff for particular nutritional uses and a medical device in the applications for granting reimbursement and establishing the official selling price and increasing the official selling price, which do not have a reimbursed equivalent in a given

indication (Dz. U. /Journal of Laws/ of 2021, item 74). The Agency performed its own calculations assuming no differences in treatment efficacy.

The estimated value of the official selling price (OSP) of Mavenclad, at which the cost of its application is not higher than the cost of application of the technology currently reimbursed in the indication analysed with the most favourable cost-effectiveness ratio (glatiramer acetate was adopted in the analysis) is [information protected as a trade secret] for a pack of 1 tablet à 10 mg, [information protected as a trade secret] for a pack of 4 tablets à 10 mg and [information protected as a trade secret] for a pack of 6 tablets à 10 mg.

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 (BIA) was performed to estimate the public payer (NHF) expenditure in case of a positive decision on public funding of Mavenclad (cladribine) for patients at an earlier stage of the disease, i.e. extending the availability of therapy from that available only under the B.46 drug programme to that available also in the drug programme [information protected as a trade secret].

The analysis was performed only from the public payer perspective (NHF), as the results of the joint perspective (NHF and recipient) are the same. A two-year time horizon was adopted.

Two scenarios were compared: the existing and the new one. The existing scenario depicted the current situation in which the proposed technology is publicly funded in the B.46 drug programme. The new scenario includes a situation where Mavenclad will be reimbursed under the B.46 drug programme and [information protected as a trade secret], i.e. will partially take over the shares of technologies currently reimbursed under [information protected as a trade secret].

The number of patients treated under the B.29 and B.46 drug programme in 2020 is approximately 16,000. It is estimated that the overall population of RRMS patients in Poland is approximately 29,400. The applicant estimated the population size by summing the following patient groups: [information protected as a trade secret]. In the existing scenario, the proposed technology is used by 92 patients (out of 1,883 total patients treated under the B.46 drug programme in 2020). In the new scenario, the number of patients who will meet the new criteria for cladribine application was estimated to be approximately [information protected as a trade secret] in both the first and second year of analysis.

In the variant without the RSS, the total expenditure in the target population will increase in the probable market share variant by [information protected as a trade secret] during the 1st year of the reimbursement period and by [information protected as a trade secret] during the 2nd year of the reimbursement period. The corresponding values when the RSS is considered will be: [information protected as a trade secret] during the 1st year of the reimbursement period and [information protected as a trade secret] during the 2nd year of the reimbursement period.

As part of the BIA, the applicant conducted an analysis of alternative scenarios. The lowest

incremental expenditure occurs in the variant with the assumption [information protected as a trade secret], while the highest incremental expenditure [information protected as a trade secret].

Limitations

The main limitation of the analysis is the estimation of the population that will use the proposed technology on the basis of the results of a survey conducted by the applicant among specialists in neurology. The experts were presented with [information protected as a trade secret].

Other limitations are presented in the Agency Verification Analysis.

Comments on the proposed risk-sharing scheme

No remarks.

Comments on the drug programme

Following the comments received from the experts, it is suggested to [information protected as a trade secret] because it introduces more lenient criteria for cladribine treatment eligibility compared to the qualification for the application of other drugs in the drug programme [information protected as a trade secret].

It is suggested that consideration be given to merging the existing multiple sclerosis treatment programmes (and B.46 [information protected as a trade secret]) into a single programme reflecting European recommendations and to reviewing the criteria for the population treated with each technology.

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.

The proposed mechanism consists of [information protected as a trade secret]

Overview of recommendations in relation to the assessed technology

Clinical recommendations

According to clinical recommendations, the main aim of treatment for multiple sclerosis is to prevent disability progression. For this reason, it is recommended to start therapy as soon as the diagnosis is established. According to the Polish PTN 2016 guidelines, disease-modifying drugs are recommended for patients with RRMS. First-line drugs include: IFNb, GA, dimethyl fumarate and teriflunomide, while second-line treatment includes: natalizumab, fingolimod, mitoxantrone, alemtuzumab.

In the active form of RRMS, the following preparations are recommended: interferon beta-1b, interferon beta-1a, peginterferon beta-1a, glatiramer acetate, teriflunomide, fumarate dimethyl, cladribine, fingolimod, daclizumab, natalizumab and alemtuzumab, ocrelizumab, ofatumumab (ECTRIMS EAN 2018).

If signs of disease activity are present despite treatment with interferon or glatiramer acetate (relapses and/or progression of disability and/or activity confirmed by MRI imagining after 6/12 months), a more effective treatment is recommended. In this case, alemtuzumab, fingolimod or natalizumab (ECTRIMS EAN 2018) is mentioned.

Cladribine tablets are recommended as a treatment option: in patients with rapidly evolving severe (RES) RRMS defined as having had at least two relapses in the previous year and observing at least one gadolinium-enhanced lesion in the T1 sequence (on initial MRI imagining) and in patients with

RRMS after failure of previous treatment, defined as having had at least one relapse in the previous year and active lesions on MRI imaging (NICE 2021).

According to one recommendation (Prescrire 2018), cladribine tablets are not recommended in the active form of RRMS due to insufficient evidence of efficacy to justify serious side effects of the drug, including infection and cancer.

Reimbursement recommendations

Eight reimbursement recommendations related to the assessed technology were identified: The recommendations mainly highlight the cost-effectiveness of treatment relative to placebo (NCPE 2018, NICE 2019, PBAC 2018), the superiority in efficacy of cladribine tablets compared to placebo (CADTH 2018, NICE 2019, SMC 2018) and the similar therapeutic value of fingolimod (ZIN 2018). A positive recommendation was also made while reporting no proven additional benefits of cladribine tablets compared to comparators (HAS 2020, GBA/IQWIG 2018).

According to the information provided by the applicant, Mavenclad is financed [information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared under the order of the Minister of Health of 6 September 2021 (letters: PLR.4500.548.2021.13.PBO, PLR.4500.549.2021.13.PBO, PLR.4500.550.2021.14.PBO) on the preparation of President's recommendation on the assessment of: Mavenclad, Cladribinum, tablets, 10 mg, 1, tablet, EAN code: 04054839365331; Mavenclad, Cladribinum, tablets, 10 mg, 4, tablet, EAN code: 04054839365348; Mavenclad, Cladribinum, Tablets, 10 mg, 6, tablet, EAN code: 04054839365355, in the indication: under the drug programme [information protected as a trade secret], 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. 127/2021 of 22 November 2021 on the assessment of Mavenclad (cladribinum) under the drug programme for the treatment of multiple sclerosis (ICD-10 G35).

References

1. Position of the Transparency Council No. 127/2021 of 22 November 2021 on the assessment of Mavenclad (cladribinum) under the drug programme for the treatment of multiple sclerosis (ICD-10 G35).
2. Report No. OT.4231.39.2021 "Application for the reimbursement and establishment of the official selling price of Mavenclad (cladribine) under the drug programme Treatment of Multiple Sclerosis (ICD-10 G35) Verification analysis" Date of completion: 10 November 2021.