REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Mavenclad
10 mg tablet x 1
10 mg tablet x 4
cladribine

Therapeutic indication(s)	Indicated as a first-line treatment of relapsing-remitting multiple sclerosis (MS).
Start/end date of procedure	26.11.2019 – 04.06.2020
Final decision	Rejects inclusion of therapeutic indication in Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF).

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Mavenclad

Health problem

Multiple sclerosis (MS) is an autoimmune disease with a genetic predisposition, which in combination with certain environmental factors leads to a cascade of immune responses and disruption of the blood-brain barrier. As a result, inflammatory demyelination of the white matter in the central nervous system (CNS) occurs (the protective sheath of the nerve cells is destroyed), leading to neurological deficit. The clinical course is heterogeneous, characterized by occurrence of transient or progressive damage. MS is classified into four subtypes, defined on the basis of disease progression and clinical manifestation. In approximately 85-90% of MS patients the disease onset is in relapsing-remitting form (RRMS). A significant percentage of patients in 10-15 years develop secondary progressive form (SPMS). The remaining 10-15% have a primary progressive form (PPMS) with a slow and disabling progression from the beginning. Small percentage (about 5%) of the cases have a progressive-relapsing form (PRMS) of multiple sclerosis. Permanent disability in patients is due to neuron degeneration.

The clinical course is characterized by scattered transient or progressive neurological symptoms (pyramidal, coordination, sensory, pelvic-reservoir disorders, etc.).

The disease commonly begins with visual or motor symptoms (49%), followed by limb paresis or paresthesias (42%), coordination (23%) or pelvic-reservoir (10%) disorders. Symptoms may occur individually or in combination (30 to 50% of patients). In the course of the disease all patients will eventually develop visual or oculomotor symptoms, limb paresis or paresthesias (88%), coordination (82%), pelvic-reservoir (63%) or cognitive (40%) disorders.

In patients with RRMS, the disease clinical manifestations consist of relapses and disease progression. Relapses are defined as periodic disease exacerbations in which new or existing clinical symptoms occur, increasing the severity of disability for a certain period of time and followed by partial or complete recovery (remission phase). Disease progression is associated with increasing permanent disability without periods of remission. The quality of life in patients with PRMS worsens progressively as disease progresses. Within 10 years from disease onset, in 70% of patients MS will progress from relapsing-remitting form to a secondary progressive form, characterized by high degree of disability.

Mavenclad (cladribine) health technology is indicated for the treatment of adult patients with highly active PRMS, diagnosed according to clinical characteristics and imaging. Presently,

the treatment of PRMS with cladribine is paid by the NHIF and is reimbursed as a second-line treatment. This assessment focuses on the use of Mavenclad as first-line therapy.

Epidemiological data

Data on disease incidence indicate that in Bulgaria about 3600 people are afflicted, and each year 80 new individuals get sick. According to data from recent years, the prevalence in neighboring countries and in high-risk Central European areas is growing and surpasses 100/100 000 people. The increase in morbidity and morbidity is linked with better and earlier diagnosis and reduced mortality. MS predominantly affects young people, mostly between 30 - 34 years of age. From 3 to 10% of MS cases begin in childhood and adolescence. The predisposition of females to the disease is twice as high.

Efficacy data

To evaluate the therapeutic efficacy and safety of cladribine, the results of four main clinical trials (CLARITY, CLARITY EXT, ORACLE-MS, ONWARD), an ongoing observational study (PREMIERE) and an analysis of the comparative efficacy of cladribine with other treatments were compared and analyzed.

CLARITY clinical trial - evaluates the therapeutic efficacy and safety profile of cladribine oral tablets in patients with relapsing-remitting MS (RRMS). **CLARITY EXT** clinical trial - evaluates therapeutic efficacy and safety profile of cladribine oral tablets in patients with RRMS who have completed a previous CLARITY clinical trial. Data from both studies show a convincing advantage of cladribine tablets over placebo, but comparative efficacy data versus alternative therapies are lacking, as in the study design no alternative medicinal product is included. The data from the CLARITY and CLARITY EXT registration studies do not substantiate positioning of the health technology Mavenclad as a first line therapy.

ORACLE MS clinical trial - examines therapeutic efficacy and safety profile of cladribine oral tablets in patients after the first clinical manifestation of demyelination during transition to clinically defined multiple sclerosis (CDMS). It includes patients with first manifestation of demyelination. The data from the ORACLE study confirm the benefits of cladribine tablets over placebo in patients with first manifestation of demyelination as well as the risk reduction in transition to clinically defined multiple sclerosis in narrow indications, not subject to treatment in Bulgaria. The results of the study do not substantiate the positioning of the health technology Mavenclad as a first line therapy.

ONWARDS clinical trial - evaluates the therapeutic efficacy and safety profile of cladribine oral tablets in combination with IFN-β for the treatment of patients with RRMS. It includes patients in whom IFN-β has shown incomplete efficacy, the group corresponds to patients,

unsuccessfully treated with first line agents. When comparing the results between the treated groups, the advantages of monotherapy with cladribine tablets over that with IFN-β were ascertained, which supports the affiliation of cladribine tablets to the group of more effective therapies, thus supporting Mavenclad's association with second-line treatment.

Due to the lack of direct comparisons of cladribine to other DMDs, several statistical approaches were used to evaluate the comparative effectiveness of cladribine tablets versus alternative DMDs:

- A systematic literature review (SLR) and network meta-analysis (NMA)

SLR results - included are 44 studies with ITT patient population and 11 studies with HRA + DAT patient population.

Network meta-analysis

ARR network analysis data show better ARR values for cladribine tablets compared to placebo and first-line therapies and at the same time comparable to line II therapies ARR-indicators.

In the comparative assessment of ARR, the data do not substantiate positioning of Mavenclad health technology in first line therapies and even support its affiliation to the second line.

- Meta-regression analysis - The results show comparable efficacy of cladribine tablets with other DMDs, which are currently positioned as a second line treatment of patients with highly active RRMS: fingolimod, natalizumab and alemtuzumab. The data do not substantiate the positioning of Mavenclad health technology in first line therapies and even support its affiliation to the second line.

Data reported by patients

There is a high level of satisfaction in patients treated with cladribine tablets. Given the high effectiveness of the therapy, its use results in reduced consumption of health resources. Comparative analysis with alternative therapies is lacking. The data do not substantiate in clinical terms the positioning of Mavenclad health technology among first line therapies.

Safety data

Adverse reactions with the greatest clinical significance in MS patients receiving cladribine at the recommended cumulative dose of 3.5 mg/kg for 2 years at clinical trials include lymphopenia and herpes zoster. The incidence of herpes zoster was higher during the period of 3rd and 4th grade lymphopenia, compared with the period when patients did not have grade 3 or 4 lymphopenia.

Cladribine tablets have a favorable safety profile, with known risks and available strategy for their management.

Data on comparators

The current treatment of patients with relapsing-remitting course of the disease is initiated with first-line medicines: beta-interferon β-1a (Avonex, Rebif and Plegridy) and β-1 b (Betaferon and Extavia), the synthetic copolymer glatiramer acetate, dimethyl fumarate and teriflunomide. These drugs are suitable for treatment initiation after the clinical debut of RRMS. Additionally, they have a relatively transient therapeutic effect and accordingly guarantee a safe transition to other therapeutic alternatives. When the potential of first-line drugs is exhausted, a switch to those of the second line is made. Switching to oral therapy only for patient's comfort is not recommended without medical grounds (subeffectiveness or intolerance).

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions intended for the health care systems of other countries
Mavenclad health technology assessments intended for the healthcare systems of Germany and the UK have been presented, which are positive.

Applied analysis
The selected method for comparative assessment of cladribine health technology is economic cost-utility analysis (CUA), health benefits have been measured as quality-adjusted life years (QALY). The perspective of the analysis is that of the paying institution – the National Health Insurance Fund (NHIF). The selected time horizon is 50 years, but it is not in line with clinical practices in Bulgaria.

Health benefits and costs are discounted at an annual discount rate of 3.5%.

Alternatives have been selected for comparison with the medicinal product Mavenclad for the treatment of patients with relapsing-remitting course of the disease as first-line medicinal product, namely beta interferon β-1a and β-1b, the synthetic copolymer glatiramer acetate, dimethyl fumarate and teriflunomide.

A cohort-based multi-state Markov model is employed for evaluating the cost-effectiveness of cladribine versus therapeutic alternatives in patients with RRMS. The applied model includes the impact on the quality of life on the progression of disability, frequency of seizures and

treatment-related ADR in a given patient with MS. The model is based on two mathematical models:
• "natural history" reference model, which was developed using data on the progression of disability and relapses in patients receiving the best supportive care.

• Therapy-adjusted model that combines the reference model with data on comparative efficacy and safety of DMD versus placebo.

The results of the cost-benefit analysis show that cladribine dominates first - line treatment alternatives in terms of health benefits and costs, with the exception of the medicinal products IFNβ-1a (Rebif 44 μg) and IFNβ-1b (Betaferon/Extavia), which show a lower cost compared to the reviewed health technology. In the model, the cost of cladribine is discounted for a shorter time horizon, as it is administered in the first 2 years of therapy, and there is no data for its use after the 4th year. When discounting of costs is applied for the whole time horizon for therapies with first - line medicinal products and with the evaluated health technology, cladribine cost is almost twice higher than alternatives.
Subgroup analysis is not applied.

Costs of the assessed health technology
Included are costs of the assessed health technology, of treatment with alternatives, of disease monitoring and follow - up, and costs of adverse drug reactions management.

Budget impact analysis
The budget impact analysis was conducted from the point of view of the payer institution – the NHIF for a time horizon of 5 years. The estimated number of patients in the first year is 60, reaching 342 in the fifth year. A sensitivity analysis through tornado diagram was performed. Reimbursement of the therapeutic indication for the first-line treatment of adult RRMS patients will lead to an increase in the cost of the payer NHIF, not taking into account risk sharing agreements and patient access schemes.

Conclusion

The results of the clinical trials do not clinically substantiate the administration of Mavenclad health technology as a first line therapy, moreover, they confirm its positioning as a second line therapy.
The presented cost-utility and budget impact analyses demonstrate a higher cost in the event the Mavenclad health technology is reimbursed as a first line treatment for RRMS. From a clinical and pharmacoeconomic point of view, there is no ground for adding an indication of first-line treatment of relapsing-remitting multiple sclerosis to current indications for use of Mavenclad (cladribine).