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

HEALTH TECHNOLOGY ASSESSMENT

Livtencity

200 mg film-coated tablet x 56 bottle HDPEN

INN Maribavir

Therapeutic indication(s)	Treatment of infection and/or disease caused by cytomegalovirus (CMV) that is refractory (with or without resistance) to one or more prior treatments, including ganciclovir, valganciclovir, cidofovir, or foscarnet in adult patients who have undergone haematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT).
Start/end date of procedure	20.07.2023 – 21.12.2023
Final decision	Inclusion in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases reimbursed by the National Health Insurance Fund (NHIF). Inclusion in Annex 2 of the Positive Drug List (PDL) for purchase by the healthcare facilities with state and/or municipality ownership and under Article 5 of the Medical Establishments Act.

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

Health problem

Cytomegalovirus (CMV) is a DNA virus from the beta-herpesvirus group, widely prevalent in the human population. Infection most commonly occurs during childhood, presenting with flu-like symptoms that usually resolve without complications. The virus remains in a latent phase (non-replicating) within the body, persisting in various tissue cells such as epithelial, endothelial, smooth muscle, macrophages, dendritic cells, lymphocytes, fibroblasts, myeloid progenitors, and others. Antibodies have a lesser role in protecting against CMV, limiting to some extent the infection of new cells. IgG antibodies remain a marker of encounter in the body for life, with people who have encountered CMV (whether there has been clinical manifestation or not) being IgG (+) positive or seropositive and the rest being IgG (-) negative - seronegative. If left uncontrolled, CMV infection leads in a large percentage of cases to often fatal CMV disease, and even when it does not, the prognosis is significantly worse and patient survival is reduced.

During allogeneic hematopoietic stem cell transplantation (allo-HSCT), the recipient's immune system is replaced by that of the donor and immunosuppressive therapy is administered to prevent graft versus host disease (GvHD) – where the donor's immune system attacks the recipient's normal tissues/organs. Patients after allo-HSCT represent some of the most severely immunocompromised patients in medicine in general. For comparison, in the final stage of acquired immunodeficiency syndrome (AIDS) as a result from a HIV infection, the CD4+ T-cell count must be below 200/microliter. In allo-HSCT patients, the median period to reach 200 CD4+ T-cells/microliter is around the third month, and in addition to the extremely low numbers, patients are on additional immunosuppression with a calcineurin inhibitor and an antimetabolite. As a consequence of over 90% seropositivity for CMV in Bulgaria, virtually all patients undergoing allo-THCS in our country are at risk of CMV reactivation and the fatal consequences that can result.

Maribavir is the only product indicated for refractory CMV infection and fills in a huge therapeutic gap.

Epidemiological Data

The incidence of CMV infection (reactivation) in Bulgaria is approximately 70-80% (similar to other countries with the same seropositivity rate) among seropositive patients after allo-HSCT (in the absence of prophylaxis with Letermovir).

Efficacy data

Maribavir's therapeutic efficacy and safety profile have been analyzed in two clinical trials.

Clinical Trial TAK-620-202 (Phase II, NCT01611974) is a phase II randomized trial evaluating the safety and anticytomegalovirus (CMV) activity of various doses of maribavir for the treatment of CMV infections that are resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet in transplant recipients. The results show that 67% of patients had confirmed undetectable plasma CMV DNA within 6 weeks after starting treatment, which was the primary endpoint. There was no significant differentiation between the three dosing regimens of maribavir. All doses were equally effective in clearing CMV viremia based on the proportion of patients with confirmed undetectable plasma CMV DNA within 6 weeks after starting treatment.

Clinical Trial TAK-620-303/SOLSTICE (Phase III, NCT02931539) is a multicenter, randomized, open-label, active-controlled superiority Phase III trial comparing 8 weeks of treatment with maribavir versus investigator-assigned treatment (IAT; conventional antiviral therapy) in HSCT and SOT patients with CMV infections which are refractory (with or without resistance) to one or a combination of conventional antiviral therapies: ganciclovir, valganciclovir, foscarnet, or cidofovir. The primary endpoint was the percentage of patients who achieved clearance of CMV viremia, measured by CMV DNA concentration in plasma, at week 8. The key secondary endpoint was the percentage of participants who achieved confirmed CMV viremia clearance and control of CMV infection symptoms at the end of week 8, followed by maintenance of treatment effect at week 16.

Results showed that for the primary endpoint, maribavir outperformed IAT and a significantly higher proportion of patients achieved clearance of CMV viremia with maribavir (55.7%) versus IAT (23.9%) at week 8. The primary endpoint required confirmed viremia clearance with two consecutive negative CMV DNA samples separated by at least 5 days. More patients treated with maribavir demonstrated sustained clearance of viremia and control of symptoms in refractory (with or without resistance) CMV compared to conventional therapies in the direct SOLSTICE Phase III trial. More maribavir-treated patients achieved CMV viremia clearance and control of CMV infection symptoms at week 8 and maintained it through week 16. A higher percentage of patients on maribavir achieved the key secondary endpoint, clearance of CMV viremia, and control of symptoms by the end of week 8, maintained through week 16 (18.7% for maribavir vs. 10.3% for IAT). Additionally, when patients in the IAT group who received alternative anti-CMV treatment before week 8 were also counted as responders, the response rate in the IAT group increased from 10.3% to 12.8%, still below the response rate in the maribavir group (18.7%), which did not require such an adjustment.

Safety data

The most commonly reported adverse reactions occurring in at least 10% of participants in the maribavir group were: taste disturbances (46%), nausea (21%), diarrhea (19%), vomiting (14%), and fatigue (12%).

Data on comparators

Therapeutic alternatives are switching the first-line agent (val)ganciclovir to foscarnet and vice versa or cidofovir. All three alternatives are not indicated for the treatment of patients with refractory CMV infection.

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions intended for the health care systems of other countries

Four evaluations have been published by other government institutions - The National Institute for Health and Care Excellence - NICE (Great Britain), Haute Autorité de santé - HAS (France), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen - IQWiG (Germany) and the Canadian Agency for Drugs and Technologies in Health - CADTH (Canada), all recommending that Livtencity Health Technology to be reimbursed for the indication.

Applied analysis

The pharmacoeconomic analysis was applied in the form of cost-effectiveness analysis (CEA), in which the final result in terms of health benefits is presented in the form of life year gained (LYG) and cost utility analysis (CUA) in which the final outcome in terms of health benefits is presented in the form of quality-adjusted life years (QALY) gained. Ganciclovir, oral valganciclovir, foscarnet, cidofovir were selected as comparative alternatives. The perspective of the analysis is that of the paying institution - the National Health Insurance Fund (NHIF) and the Ministry of Health (MOH). The chosen time horizon is lifetime (40 years). Costs and results are discounted at an annual discount rate of 3.5%. The chosen modeling method is a Markov model divided into two stages:

• Stage 1: 0 to 12 months

Markov model with three states: clinically significant CMV infection (csCMV), no clinically significant CMV infection (n-csCMV) and dead state.

• Stage 2: 12 months to life horizon

Two-state Markov model, with the states being alive or dead. The time horizon represents a lifetime with 4-week cycles for the first 3 years, then 1-year cycles.

The results of the analysis show that the calculated incremental cost-effectiveness ratios are above the threshold for favorable cost-effectiveness of BGN 60,636 (3 times GDP per capita according to NSI data for 2021), which defines the therapy as cost-ineffective.

Subgroup analyses
None applied.

Costs for the assessed health technology
The model included costs of pharmacotherapy with Livtencity (maribavir), costs of pharmacotherapy with comparator alternatives, costs of medical activities, additional medical activities in disease control, costs of adverse event control, and costs of diagnosis and treatment of the living donor and of the recipient in the post-transplantation period, paid by the Ministry of Health.

Budget impact analysis
The analysis of the budget impact was conducted from the perspective of the paying institution - NHIF. The perspective of the Ministry of Health is also presented informatively, as there is a reimbursement of costs for transplantation activities. The time horizon is 5 years. The target population includes adult patients who have undergone hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT) with cytomegalovirus (CMV) infection and/or disease who are refractory (with or without resistance) to one or more prior treatments, including ganciclovir, valganciclovir, cidofovir, or foscarnet. For the purposes of the analysis, the following alternative was selected: Valcyte (valganciclovir). The estimated number of patients in the first year is 5, and in the fifth year – 8. The budget impact analysis was conducted, developing 2 scenarios "World with Livtencity" and "World without Livtencity".

The analysis projects an increase in costs over a five-year period to NHIFs, excluding risk-sharing agreements and patient access schemes.

Conclusion

Livtencity (Maribavir) is the only product approved by regulatory agencies for the treatment of refractory CMV infection/disease in transplant patients, thus addressing unmet patient needs. Livtnecity is more effective than available treatment options and has a favorable safety profile that allows treatm ent of CMV infection/disease without having to interrupt therapy due to severe organ toxicity. The budget impact analysis shows that the usage of Livtencity healthcare technology will result in increased costs for the paying institution.