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

HEALTH TECHNOLOGY ASSESSMENT

Dovato

50 mg/300 mg film-coated tablet x 30

dolutegravir/lamivudine

Therapeutic indication(s)	Indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.
Start/end date of procedure	21.02.2020 – 30.09.2020
Final decision	Inclusion in the Positive Drug List (PDL): - Annex 2 for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act; - Annex 3 for the treatment of diseases paid for from the budget of the Ministry of Health.

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

Health problem

Human immunodeficiency virus (HIV) is an RNA virus belonging to the family of retroviruses (Retroviridae). HIV enters the host cells (specifically CD4 T-helper lymphocytes and macrophages), where several important enzymes are involved in its replication cycle: reverse transcriptase, protease and integrase. The virus is transmitted by direct contact of mucosa or bloodstream with body fluid (blood, semen, vaginal fluid and breast milk) containing virus particles.

The diagnosis of the disease is based on epidemiological, clinical and laboratory data. Laboratory tests are screening (primary) and confirmatory. After a positive screening test, a confirmatory test must be performed, which excludes the possibility of a false positive result.

Dovato is a fixed-dose combination for the treatment of HIV infection containing an integrase inhibitor (Dolutegravir) and a nucleoside inhibitor (Lamivudine). Dovato (dolutegravir/lamivudine) is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents over 12 years of age, weighing at least 40 kg, without known or suspected resistance to the integrase inhibitors class or to lamivudine.

Epidemiological data

Human immunodeficiency virus (HIV) infection continues to be a global problem due to its pandemic nature and unattainability of complete cure. Approximately 0.8% (0.7-0.9%) of people between the ages of 15 and 49 are infected with HIV globally, and the spread of the infection varies from region to region. Bulgaria is one of the countries that still has a low incidence of the disease - 0.4%. The HIV (+) patients registered so far in Bulgaria (deceased included) are about 3320. About 1800 patients are currently being monitored in acquired immune deficiency wards in the country, and over 90% of them are on antiretroviral therapy.

Efficacy data

To evaluate the therapeutic efficacy and safety of dolutegravir/lamivudine, the results of two main ongoing clinical trials (Gemini-1 and Gemini-2) in treatment-naïve patients, one ongoing study in virologically suppressed patients (TANGO), one network meta-analysis, as well as a meta-analysis of the efficacy and safety of real world data were compared and analyzed.

Clinical trials GEMINI-1 and GEMINI-2
Clinical trials GEMINI-1 and GEMINI-2 are identical (twin studies), phase III, randomized, double-blind, multicenter, parallel-group studies with active control to assess non-inferiority.

A rapid reduction in viral load with a median virologic suppression time of 29 days was observed in both treatment groups. Both studies demonstrated non-inferiority of dolutegravir/lamivudine vs dolutegravir + tenofovir/emtricitabine. The results showed similar therapeutic efficacy (> 90% with HIV-1 RNA < 50 copies/μl at week 48), regardless of the baseline virologic load. The results are similar in high virologic load and in patients with higher CD4 cell counts.

TANGO clinical trial
The TANGO clinical trial was a phase 3, 200-week, randomized, open-label, multicenter, active control, parallel-group study to evaluate the non-inferior antiretroviral efficacy and safety of replacing tenofovir-based regimens with dolutegravir/lamivudine therapy in adult patients with HIV-1 infection who are virologically suppressed and stable on tenofovir-based regimens.

The corrected difference in the proportion of patients with virologic failure between dolutegravir/lamivudine and tenofovir-based treatment arm regimens was -0.3, demonstrating non-inferiority.

Network meta-analysis
The results for the primary endpoint of all treatment regimens included in the NMA showed that at week 48, the rate of virological suppression of dolutegravir/lamivudine did not differ significantly from that of most other regimens, recommended for first-line treatment, including dolutegravir + abacavir/lamivudine, dolutegravir + tenofovir/emtricitabine, bictegravir + tenofovir/emtricitabine, elvitegravir/cobicistat+tenofovir/emtricitabine, darunavir/iritonavir + tenofovir/emcitrabine and rilpivirine + tenofovir/emtricitabine, while being superior to efavirenz/tenofovir/emtricitabine. The likelihood of more patients reaching virological suppression at week 48 was higher with dolutegravir/lamivudine than with all other triple regimens (53.0 - 98.6%), with the exception of dolutegravir + tenofovir disoproxil fumarate/emtricitabine (11.4%) and dolutegravir + teno. alafenamide/emtricitabine (26.2%).

Safety data

The most severe adverse reaction reported with dolutegravir is a hypersensitivity reaction that includes rash and severe hepatic impairment. Very common and common side effects are: headache, nausea, diarrhea, insomnia, depression, anxiety, abnormal dreams, dizziness,

drowsiness, vomiting, abdominal pain, flatulence, rash, itching, alopecia, arthralgia, muscle damage, fatigue, increased CPK, ALAT, ASAT.

Data on comparators

Based on clinical trials evaluating the efficacy and safety of Dovato, the following alternatives could be partially or completely displaced by the introduction of the new technology:
- darunavir/cobicistat + emtricitabine/tenofovir disoproxil
- darunavir/cobicistat + abacavir/lamivudine
- raltegravir + abacavir/lamivudine
- raltegravir + emtricitabine/tenofovir disoproxil
- dolutegravir + emtricitabine/tenofovir disoproxil

Pharmacoeconomic indicators

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

Publicly available assessments of Dovato health technology have been performed for the health care systems of Scotland by SMC and Germany by G-BA, with a positive decision from SMC and a negative decision from G-BA.

Applied analysis
An analysis was performed to evaluate the cost effectiveness of the fixed-dose dolutegravir/lamivudine regimen in previously untreated patients. The perspective set in the analysis is of the payer - the Ministry of Health. Comparators used are: a free combination of dolutegravir and lamivudine, dolutegravir + tenofovir disoproxil/emtricitabine, raltegravir + tenofovir disoproxil/emtricitabine, darunavir/cobicistat + emtricitabine/tenofovir disoproxil.

The time horizon is one year. A cost-minimization pharmacoeconomic analysis (CMA) was employed. The outcome measures were virologic suppression achieved at week 48 of treatment initiation, mean change in CD4 + cell count (cells/μl) from baseline, and proportion of patients with drug-related adverse reactions and annual cost savings. Discounting and modeling have not been applied. The administration of the applicant health technology Dovato (dolutegravir/lamivudine) in previously untreated patients will save costs compared to the combined treatment regimens. The single tablet fixed dose dolutegravir/lamivudine has an identical annual cost compared to the co-administration of individually combined dolutegravir and lamivudine.

A probabilistic sensitivity analysis was performed, confirming the conclusions in the main analysis.

Costs for the assessed health technology

The costs for the applicant health technology and the reviewed alternatives are presented.

Budget impact analysis

The perspective of the analysis is that of the payer - the Ministry of Health. The time horizon of the budget impact analysis is 5 years.

The target population in the present analysis included adult patients and adolescents over 12 years of age, weighing at least 40 kg, infected with human immunodeficiency virus type 1 (HIV-1), without known or suspected resistance to the class of integrase inhibitors or to lamivudine.

The reimbursement of the new technology by the Ministry of Health will lead to cost savings in all cases considered, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Dovato (dolutegravir/lamivudine) is a fixed-dose combination indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents over 12 years of age, weighing at least 40 kg, without known or suspected resistance to the integrase inhibitor class or to lamivudine. Dovato (dolutegravir/lamivudine) use results in viral suppression regardless of prior therapy, has high antiretroviral activity, a high barrier to resistance, a favorable pharmacokinetic/pharmacodynamic profile, few drug interactions and a lower frequency of long-term toxicity. As a single fixed-dose tablet, Dovato improves patients' adherence to therapy, which in turn increases the benefits of treatment. The use of Dovato (dolutegravir/lamivudine) in treatment-naïve patients will save costs compared to combination regimens. The inclusion of the new technology in the Positive Drug List will lead to cost savings in all cases considered.