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

HEALTH TECHNOLOGY ASSESSMENT

Delstrigo

100mg/300mg/245mg film-coated tablet x 30

doravirine/lamivudine/tenofovir disoproxil

Therapeutic indication(s)	Indicated for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine, or tenofovir.
Start/end date of procedure	27.09.2019 – 18.06.2020
Final decision	Inclusion in Annex 3 of the Positive Drug List (PDL) for the treatment of diseases paid 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 Delstrigo

Health problem

HIV infection: The human immunodeficiency virus (HIV) is an RNA virus that belongs to the family of retroviruses (Retroviridae). HIV is characterized by a prolonged latent course of infection and the formation of viral depots in the CNS, lymphatic structures and gastrointestinal tract. HIV generally infects CD4 + T cells, leading to immune suppression and, in the absence of therapy, to a fatal outcome due to an increased risk of infection with other viruses, bacteria, parasites and fungi, as well as neoplastic processes (AIDS-defining diseases). The diagnosis of the disease is based on epidemiological, clinical and laboratory data. Clinical symptoms may not occur in all patients. During acute HIV infection there is usually a high-level viremia and often a CD4 + T cells decline. After an acute infection, a certain balance is reached between viral replication and the host's immune response, and many of those infected may not have clinical manifestations of the disease for years. At the end of the latent period, the symptoms that develop comprise mild immunological, dermatological and neurological manifestations. Factors, related to the infected individual define whether the HIV infection will progress rapidly to severe immunosuppression or the individual will become part of the group of long-term "non-progressors", which represents about 5% of all infected patients.

The main groups of antiretroviral medicinal products are: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INSTIs), fusion inhibitors (FIs) and entry inhibitors (EIs).

The new health technology DELSTRIGO (doravirine/lamivudine/tenofovir disoproxil fumarate) is a fixed-dose tablet antiretroviral therapy, indicated for the treatment of treatment-naïve HIV-1 infected adults without previous or current evidence of resistance to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs), lamivudine or tenofovir, to maintain normal CD4 + T cell levels. DELSTRIGO is also indicated for the treatment of patients switching from another ART (antiretroviral therapy) to DELSTRIGO.
Good efficacy and a favorable safety profile define DOR/3TC/TDF (DELSTRIGO) as a new therapeutic option for HIV-1 infected patients.

Epidemiological data

Bulgaria is one of the countries that still has a low incidence of the disease - 0.4%. So far, the registered HIV (+) patients in Bulgaria (deceased included) are about 3150.

Efficacy data

To assess the therapeutic efficacy and safety profile of doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) for the treatment of adult HIV-1 infected patients, previously untreated with antiretroviral therapy (ART), the results of two clinical trials and one indirect comparison have been compared and analyzed.

DRIVE-AHEAD clinical trial (NCT02403674)
Evaluates the efficacy and safety of doravirine/lamivudine/tenofovir disoproxil fumarate once daily compared to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment naïve HIV-1 infected individuals. It is a phase 3 multicenter, double-blind, actively controlled, randomized clinical trial to assess non-inferiority.

The proportion of patients who reached the primary endpoint of HIV-1RNA < 50 copies/mL at week 48 was 84.3% in the doravirine/lamivudine/tenofovir disoproxil fumarate group and 80.8% in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group. The results show that the antiretroviral efficacy in the doravirine/lamivudine/tenofovir disoproxil fumarate group was not lower than in the efavirenz/emtricitabine/tenofovir disoproxil fumarate group.

The virological results of DOR/3TC/TDF were comparable to those of EFV/FTC/TDF for the proportion of patients with HIV-1 RNA < 50 copies/mL (84.3% vs. 80.8%, respectively) and HIV-1 RNA ≥ 50 copies/mL (10.7% vs. 10.2%).
The change from baseline in CD4 + T-lymphocyte counts was similar for both treatment groups. The mean increase from baseline at week 48 was 198 cells/mm3 in the DOR/3TC/TDF group and 188 cells/mm3 in the EFV/FTC/TDF group.

DRIVE-SHIFT clinical trial (NCT02397096)
Evaluates viral suppression through week 48 when switching to doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF). A multicenter, open-label, randomized, active-controlled clinical trial to evaluate the switch from a stable antiretroviral therapy regimen to a fixed-dose combination DOR/3TC/TDF. Patients (n = 673) were randomized in a 2: 1 ratio to immediate switch to DOR/3TC/TDF on day 1 or to a delayed switch to DOR/3TC /TDF at week 24. The delayed switch group remained in its initial mode until transition to DOR/3TC/TDF in the 24th week. The trial consisted of a 48-week baseline period, followed by a 96-week open-label phase (extension), in which all patients received DOR/3TC/ TDF. DOR/3TC/TDF was taken orally once a day.

At week 24, the proportion of participants with HIV-1RNA < 50 copies/mL was 93.7% in the immediate switch group and 94.6% in the delayed switch group. At week 48, HIV-1 RNA levels < 50 copies/mL were maintained in 90.8% of patients with immediate switch,

indicating that efficacy was non-inferior when switching to another treatment than if the baseline regimen was continued for 24 weeks. Of the 209 delayed switch participants who switched to DOR/3TC/TDF at week 24, 198 (94.7%) had HIV-1RNA < 50 copies/mL at week 48.

Indirect comparison for evaluation of DOR/3TC/TDF versus DTG + 2NRTI in untreated HIV-1 infected patients

The following studies have been identified: **DRIVE-AHEAD** (DOR/3TC/TDF versus EFV/TDF/FTC), **SPRING-1** (DTG + [ABC/3TC or TDF/FTC] versus EFV + [ABC/3TC or TDF/FTC]) and **SINGLE** (DTG + ABC/3TC vs. EFV/TDF/FTC). The studies are comparable in terms of design, patient characteristics and research question. The indirect comparison of DOR/3TC/TDF with DTG + 2NRTI was performed versus the common comparator EFV + 2NRTI.

The indirect comparison of DOR/3TC/TDF to DTG + 2NRTI did not show a statistically significant difference in virologic response at week 96.

An indirect comparison of DOR/3TC/TDF versus DTG + 2NRTI in treatment naïve HIV-1 infected patients showed a statistically significant difference in CD4 cell count at week 96.

The results of the indirect comparison of DOR/3TC/TDF to DTG + 2NRTI using the common comparator EFV + 2NRTI show comparable efficacy in terms of virologic response and improvement in CD4 cell count, with no statistical significance achieved for both endpoints.

Data reported by patients

Clinical study DRIVE-AHEAD (NCT02403674)

General health outcomes indicate that there are no statistically significant differences between the groups in terms of absenteeism, presenteeism, health-related overall deterioration of work productivity or daily activities at all time points.

Statistically significant differences were found for some results, such as an average increase in the score for health-related overall deterioration of work productivity, an average decrease in the score for per cent overall work impairment due to ill-health and others.

Safety data

The most common side effects include fatigue, fever, abnormal dreams, insomnia, nightmares, depression, headache, dizziness, drowsiness, cough, nasal symptoms, nausea, diarrhea, stomach pain, vomiting, alopecia, rash, muscle disorders.

Data on comparators

The medicinal product Triumeq (Dolutegravir/Abacavir/Lamivudine) was chosen as comparator, indicated for the treatment of adults and adolescents over 12 years of age with a

body weight of at least 40 kg, infected with human immunodeficiency virus (HIV). DTG/ABC/3TC is a fixed dose tablet.

Pharmacoeconomic indicators

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

Assessments of the reviewed health technology have been made publicly available by HAS, G-BA and CADTH, which recommend its reimbursement, with CADTH imposing a condition regarding the total cost of treatment.

Applied analysis

A cost-minimisation pharmacoeconomic method was employed using the virologic response at week 96 and CD4 cell count at week 96 as indicators of efficacy. Indirect comparisons of Delstrigo to DTG + 2NRTI performed in previously untreated and virologically suppressed patients infected with human immunodeficiency HIV-1, did not show statistically significant differences in terms of therapeutic efficacy. The dosage and route of administration of drug therapies in patients with/without prior treatment are the same. An advantage of the new health technology is the fixed dose combination, which reduces the so-called "pill burden" and ensures a higher degree of adherence to therapy, which is important for reducing resistance to antiretroviral therapy.

The perspective of the analysis is that of the paying institution - MH. The comparator is the INSTI-based fixed triple combination - dolutegravir/abacavir/lamivudine (Triumeq).

The results of the presented analysis show that the inclusion of DELSTRIGO in the PDL is associated with a reduction in costs compared to the treatment alternative Triumeq. A sensitivity analysis has also been presented, demonstrating the validity of the results of the analysis, DELSTRIGO maintains a lower cost of treatment per patient compared to Triumeq.

Costs for the assessed health technology

Only direct medication-related costs have been included.

Budget impact analysis

The budget impact analysis was conducted from the point of view of the paying institution - MH. The time horizon is 5 years. The target population includes adult patients infected with human immunodeficiency virus HIV-1 without previous or current evidence of resistance to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs), lamivudine or tenofovir, both treatment naïve patients and virologically suppressed patients switching from previous antiretroviral therapy (ART) to DELSTRIGO.

The total number of treatment naïve patients eligible for the new health technology is projected to be 20 in the first year, reaching 68 in the fifth year. The same estimated number of patients is included in the group of treatment-experienced patients.

A sensitivity analysis using a tornado diagram in treatment naïve and treatment-experienced patients was employed, which showed that the costs were most sensitive to the variation in the price of DELSTRIGO and other therapeutic alternatives.

The budget impact analysis shows that the inclusion of the medicinal product DELSTRIGO in Annex 3 of the PDL is associated with a reduction in the cost of treatment of HIV-1 infected patients, both treatment naïve and previously treated with highly active antiretroviral therapy, compared to a reimbursed fixed dose combination, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The new health technology DELSTRIGO (doravirine/lamivudine/tenofovir disoproxil fumarate) is a fixed-dose tablet antiretroviral therapy, indicated for the treatment of treatment naïve HIV-1 infected adults without previous or current evidence of resistance to the class of non-nucleoside inhibitor transit inhibitors. (NNRTI), lamivudine or tenofovir, to maintain normal CD4 + T cell levels. Data from studies indicate that DELSTRIGO has a high efficacy comparable to that of efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF). DELSTRIGO is a highly active therapy against HIV-1 and is effective in most NNRTI-resistance mutations. The safety profile of DELSTRIGO is more favorable than that of EFV/FTC/TDF due to the reduced risk of neuropsychiatric adverse events and a more balanced lipid profile. The inclusion of the medicinal product DELSTRIGO in Annex 3 of the PDL is associated with a reduction in the cost of therapy for HIV-1 infected patients.