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

HEALTH TECHNOLOGY ASSESSMENT

Pifeltro
100 mg film-coated tablet x 30
doravirine

Therapeutic indication(s)	Indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of resistance to the NNRTI class.
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 Pifeltro

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 a bodily fluid (blood, semen, vaginal fluid and breast milk) containing virus particles. The virus is classified into two types - HIV-1, which is the predominant genotype, and HIV-2, mainly prevalent in West Africa.

Symptoms develop within days through 2 or 3 weeks of HIV contraction: fever, lymphadenopathy, pharyngitis, rash (morbilliform, maculopapular), diarrhea, headache, vomiting. Occurrence of neurological manifestations is likely, including CNS damage - aseptic meningitis, encephalitis, Guillain-Barré syndrome, cognitive impairment, movement disorders and other symptoms – easy fatigability, myalgia, arthralgia, night sweats, oral and genital ulcers. During the acute HIV infection there is usually a high level of plasma viremia, often with a marked decrease in CD4 + T cells. Subsequently, CD4 + T cells rise again, but to levels lower than those before infection. 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. In the absence of antiretroviral therapy, this period of clinical latency may last 8-10 years or more.

The diagnosis of the disease is based on epidemiological, clinical and laboratory data.

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).

Nowadays, HIV infection has become a chronic disease with a significant life expectancy of patients, provided there is adherence to appropriate antiretroviral therapy (ART). With modern ART, the life expectancy of HIV-positive individuals does not differ significantly from that of the uninfected. However, therapy should be continuous.

Epidemiological data

HIV infection continues to be a global problem due to its pandemic nature and unattainability of complete cure. Since the beginning of the epidemic, more than 70 million people have been

infected with HIV and approximately 35 million have died from HIV. According to the World Health Organization, at the end of 2017, 36.9 million people were infected with HIV, of whom 21.7 million were on antiretroviral therapy (59%). The number of newly infected in 2017 was 1.8 million, and the mortality for the year was about 940,000. Approximately 0.8% (0.7-0.9%) of people aged 15-49 are infected with HIV worldwide, with different spread of infection in different regions. Sub-Saharan Africa has the highest infection rate - 1 in 25 adults (4.4%) are infected with HIV, accounting for 70% of all HIV-positive people in the world. 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 3200.

Efficacy data

In oder to evaluate the therapeutic efficacy and safety of the health technology Pifeltro (doravirine), which in combination with other antiretrovirals is indicated for the treatment of HIV-1 infected adults without previous or current evidence of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI), the results of two clinical trials and one meta-analysis were compared and analyzed:

Clinical study *DRIVE-FORWARD (NCT02275780),* evaluating the efficacy and safety of doravirine 100 mg once daily versus darunavir 800 mg once daily plus ritonavir 100 mg once daily, each in combination with emtricitabine/tenofovir disoproxil fumarate or abacavir/lamivudine in treatment-naïve HIV-1 infected individuals.
The doravirine and darunavir + ritonavir (DRV/r) treatment groups had comparable efficacy results. The results show a non-inferior antiretroviral efficacy in the doravirine group vs the DRV+r group.

Clinical study *Protocol 007 (NCT01466985),* evaluating the safety and antiretroviral activity of doravirine plus tenofovir disoproxil fumarate/emtricitabine versus efavirenz plus tenofovir disoproxil fumarate/emtricitabine in treatment-naïve HIV-1 infected individuals.
Doravirine 100 mg shows high antiretroviral efficacy, similar to that of efavirenz at week 24, regardless of how missing data were analysed. Doravirine 100 mg also showed high and sustained antiretroviral efficacy, similar to that of efavirenz at weeks 48 and 96.

A network meta-analysis, which included studies in treatment-naïve patients, shows that there were no statistically significant differences in doravirine versus comparators in terms of viral suppression rate and mean change in CD4 + T cell count; an exception is the comparison of doravirine with darunavir + ritonavir (DRV/r), where a statistically significantly higher rate of viral suppression is seen.

Safety data

The most common side effects, considered to be treatment-related are: abnormal dreams, insomnia, nightmares, depression, headache, dizziness, drowsiness; nausea, diarrhea, stomach pain, vomiting, rash, fatigue.

Data on comparators

As comparators, drugs combining different classes of antiretroviral drugs, currently available in Bulgaria have been selected. For treatment-naive patients:

- Emtricitabine/tenofovir disoproxil + raltegravir
- Emtricitabine/tenofovir disoproxil + dolutegravir
- Emtricitabine/tenofovir disoproxil + darunavir/cobicistat
- Emtricitabine/tenofovir disoproxil + rilpivirine
- Abacavir/lamivudine + rilpivirine
- Dolutegravir/abacavir/lamivudine

For patients switching from another ART to PIFELTRO:

- Emtricitabine/tenofovir disoproxil + darunavir/cobicistat
- Abacavir/lamivudine + darunavir/cobicistat
- Emtricitabine/tenofovir disoproxil + raltegravir
- Abacavir/lamivudine + raltegravir
- Emtricitabine/tenofovir disoproxil + dolutegravir
- Dolutegravir/abacavir/lamivudine

Pharmacoeconomic indicators

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

Presented are 2 assessments of the health technology Doravirine, performed by governmental institutions for the purposes of the national health systems of Germany and France, with positive opinion, recommending reimbursement of the new technology.

Applied analysis

A cost-minimisation analysis was employed in line with the results of direct and indirect comparisons of Pifeltro (doravirine) with alternatives in adult patients infected with human immunodeficiency virus HIV-1. Costs of therapy for a one-year period were compared. The efficacy indicators used were virological response at week 96 and CD4 cell count at week 96.

The perspective of the analysis is of the paying institution – the Ministry of Helath (MH), only direct medication-related costs are included. No modeling was used in the analysis.

The results of the presented analysis show that the inclusion of Pifeltro in the PDL is associated with a reduction of costs compared to the alternatives, represented by the ones that are the most preferred in treatment-experienced/naïve patients.

Compared to the alternatives Emtricitabine/Tenofovir disoproxil + Rilpivirine and Abacavir/Lamivudine + Rilpivirine, the inclusion of Pifeltro is associated with an increase in the annual cost per patient depending on the chosen treatment regimen.

Budget impact analysis

The budget impact analysis is 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 (NNRTI). The estimated number of patients in the first year is 10, and in the fifth year the number of patients to be treated with the evaluated technology rises to 145.

The reimbursement of the new technology will lead to costs reduction without taking into account risk-sharing agreements and patient access schemes.

Conclusion

PIFELTRO (Doravirine) in combination with a backbone, containing two nucleoside analogues, reverse transcriptase inhibitors, demonstrates non-inferior efficacy compared to antiretroviral regimens employed as first-line therapy and is appropriate for reducing long-term toxicity, especially in terms of the lipid profile and CNS side effects. Data from two studies and a meta-analysis demonstrate efficacy and good tolerability in patient population, reflecting the current routine clinical practice.