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

HEALTH TECHNOLOGY ASSESSMENT

Biktarvy

50 mg/200 mg/25 mg film-coated tablet x 30

bictegravir/emtricitabine/tenofovir alafenamide

Therapeutic indication(s)	Indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.
Start/end date of procedure	15.08.2019 – 19.06.2020
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 Biktarvy

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, which is prevalent mainly in West Africa.

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). Patients with a CD4 + T cell count below 200 cells/μl or with concomitant AIDS-defining disease are defined as AIDS patients.

The diagnosis of the disease is based on epidemiological, clinical and laboratory data. Laboratory tests are divided into screening (primary) and confirmatory.

Epidemiological data

Approximately 0.8% (0.7-0.9%) of people aged between 15 and 49 years are infected with HIV globally, with different spread of infection in different regions. Bulgaria is one of the countries that still has a low frequency of the disease - 0.4%. The HIV (+) patients registered so far in Bulgaria (deceased included) are about 3200.
The usual combinations for initiating antiretroviral therapy are:

1. Two nucleoside reverse transcriptase inhibitors + one integrase inhibitor (2 NRTIs + 1 INSTI).
2. Two nucleoside reverse transcriptase inhibitors + one protease inhibitor (2 NRTIs + 1 PI).
3. Two nucleoside reverse transcriptase inhibitors + one non-nucleoside reverse transcriptase inhibitor (2 NRTIs + 1 NNRTI).

On achieving optimal viral suppression, in order to reduce long-term toxicity, combinations of two drugs are also used.

Biktarvy is a fixed dose combination for the treatment of HIV infection containing one integrase inhibitor (Bictegravir) and two nucleoside reverse transcriptase inhibitors (Emtricitabine + Tenofovir alafenamide). Bictegravir is the latest innovation in the class of integrase strand transfer inhibitors (INSTI). Biktarvy is to be taken as a single tablet dose, once daily.

Biktarvy is a comprehensive treatment regimen, indicated for the treatment of adults, infected with HIV-1 without current or previous evidence of viral resistance to integrase inhibitors, emtricitabine or tenofovir. Biktarvy is a therapeutic option, suitable for a wide range of HIV patients, including those who are co-infected with hepatitis B (HBV) or hepatitis C (HCV), patients who are positive for HLA-B * 5701 allele, and/or those with mild/moderate renal or hepatic damage. It provides a high level of viral suppression, reaching and maintaining undetectable viral load. It has a high barrier to resistance and leads to viral suppression even with suboptimal adherence to treatment, reducing the risk of virologic failure.

Efficacy data

Efficacy data were obtained from the results of six clinical trials, four of which are phase III, included were adult patients as well as adolescents in one of the studies, GS-US-380-1747.

Clinical study GS-US-380-1489

The primary efficacy endpoint was the proportion of patients with HIV-1 RNA levels < 50 copies/ml at week 48, secondary efficacy endpoint: proportion of patients with plasma HIV-1 RNA levels < 50 copies/ml at week 96. The proportion of patients with HIV-1 RNA < 50 copies/ml at week 48 (primary endpoint for efficacy) was similar for the two treatment groups B/F/TAF (BIKTARVY) and abacavir/lamivudine/dolutegravir (ABC/3TC/DTG). Non-inferior efficacy has been confirmed for B/F/TAF versus ABC/3TC/DTG. At week 96, 88% of patients in the B/F/TAF group had HIV-1 RNA levels < 50 copies/ml compared to 90% of patients in the ABC/3TC/DTG group (difference -1.9%). The therapeutic regimen B/F/TAF is non-inferior compared to the ABC/3TC/DTG regimen.

Clinical study GS-US-380-1490

The primary efficacy endpoint was the proportion of patients with HIV-1 RNA levels < 50 copies/ml at week 48. Secondary efficacy endpoints: proportion of patients with HIV-1 RNA levels < 50 copies/ml at weeks 96 and 144.

The proportion of patients with HIV-1 RNA < 50 copies/ml at week 48 (primary endpoint for efficacy) was similar for the two treatment groups B/ F/TAF (BIKTARVY) and dolutegravir +emtricitabine/tenofovir alafenamide (DTG + FTC/TAF). Non-inferiority has been confirmed for B/F/TAF versus DTG + FTC/TAF.

At week 96, 84% of patients in the B/F/TAF group had HIV-1 RNA levels < 50 copies/ml compared to 86% of patients in the DTG + FTC/TAF group (difference -2.3%). The therapeutic regimen B/F/TAF is non-inferior compared to DTG + FTC/TAF regimen.

Clinical study GS-US-380-1844

The proportion of patients with HIV-1 RNA ≥ 50 copies/ml at week 48 (primary efficacy endpoint) is similar for B/F/TAF and ABC/3TC/DTG. Switching to treatment with B/F/TAF is associated with non-inferiority versus ABC/3TC/DTG.

Clinical study GS-US-380-1747

The primary endpoint involves the calculation of plasma pharmacokinetic parameters for Bictegravir during the 24-week B/F/TAF treatment. Also calculated were the pharmacokinetic parameters of emtricitabine and tenofovir alafenamide. Efficacy was assessed at week 24 and week 48, through HIV-1 RNA levels and CD4 cell count as secondary efficacy endpoints. All included patients had HIV-1 RNA < 50 copies/ml at week 24. The mean (SD) change in CD4 cell count from baseline to week 24 was 53 (197.0) cells/µl.

Safety data

Few cases of discontinuation due to ADR in the B/F/TAF group have been reported. The most frequently reported ADR in therapeutic groups are nausea, diarrhea, headache, upper respiratory infection, rhinopharyngitis. Patients in the B/F/TAF group had fewer treatment-related ADR compared to those on comparative alternatives. Most ADR are mild or moderate in severity. No interruption of treatment was noted due to renal system-related ADR in patients in the B/F/TAF group.

Data on comparators

Combinations of antiretrovirals of different classes, currently available in Bulgaria were selected as comparators:

- Dolutegravir/Abacavir/Lamivudine (Triumeq)
- Dolutegravir + Emtricitabine/Tenofovir disoproxil
- Raltegravir + Abacavir/Lamivudine
- Raltegravir + Emtricitabine/Tenofovir disoproxil

In the analysis, the fixed dose combination Dolutegravir/Abacavir/Lamivudine (Triumeq) was selected as comparator.

Pharmacoeconomic indicators

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

Assessments of Biktarvy health technology was performed by HAS (France), SMC (Scotland), GB-A (Germany), NCPE (Ireland), GVS (Netherlands), AWMSG (Wales) and Medicinrådet (Denmark), with all these institutions approving Biktarvy for reimbursement.

Applied analysis

A pharmacoeconomic cost - minimisation analysis was performed based on data for equivalent therapeutic efficacy of Biktarvy versus Triumeq. The perspective of the analysis is of the paying institution - the Ministry of Health. The time horizon is 1 year, modeling is not applicable. Due to the short time horizon discounting has not been applied.

Comparators in the analysis are:

- the only currently existing INSTI-based fixed triple combination - dolutegravir/abacavir/lamivudine (Triumeq)
- regimens, based on an integrase inhibitor (II) in combination with a nucleoside reverse transcriptase inhibitor (NRTIs) (backbone):
  - o Isentress (RAL) + FTC/TDF (raltegravir + emtricitabine/tenofovir disoproxil)
  - o Isentress (RAL) + Kivexa (ABC/3TC) (raltegravir + abacavir/lamivudine)
  - o Tivicay (DTG) + FTC/TDF (dolutegravir + emtricitabine/tenofovir disoproxil)

The results of the analysis show that Biktarvy is associated with lower treatment costs versus comparator Triumeq on an annual basis. Compared to other alternatives, Biktarvy is associated with higher treatment costs on an annual basis.

Costs for the assessed health technology

Direct costs for drug therapy with the evaluated technology and with comparators have been presented.

Budget impact analysis

The budget impact analysis was performed from the point of view of the paying institution - the Ministry of Health, the time horizon of the analysis was 5 years. The annual number of the target population is between 699 and 1257 treatment-naïve patients and between 541 and 913 treatment-experienced patients.

Costs for treatment-naïve and treatment-experienced patients have been presented. Realization of cost savings is anticipated for the entire analyzed five - year period in the

treatment of naïve patients. When Biktarvy is used in treatment-experienced patients, increase in costs for the paying institution is anticipated, not taking into account risk-sharing agreements and patient access schemes.

Conclusion

Biktarvy (BIC/FTC/TAF) is a comprehensive treatment regimen for HIV-1, consisting of one NRTI backbone with lasting efficacy and favorable safety profile, and a new powerful INSTI with high in vitro resistance barrier and favorable pharmacokinetic profile. Analysis of the studies shows that the medicinal product has high efficiency and good safety profile. It is well tolerable, with no established association with renal, skeletal or cardiovascular side effects. It has a low potential for drug interactions and does not require dose adjustment in moderate impairment of renal function. The cost of therapy is lower than the fixed dose combination with a similar therapeutic outcome and the use of the new health technology is associated with savings of public resources.