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2021042172

Case number
2021040004

Our reference
2021042172

Your reference
CIBG-21-02629

Your letter of
12 October 2021

Date 1 December 2021
Subject GVS assessment Rukobia® (fostemsavir)

Dear Mr Blokhuis,

In your letter of 12 October 2021 (CIBG-21-02629), you asked the National Health Care Institute to assess whether the product Rukobia® 600 mg tablet with prolonged release can be included in the Medicine Reimbursement System (GVS).

HIV-inhibition drugs have held a special place in the GVS since the year 2000. On 30 March 2000, one of your predecessors stated that all antiretroviral drugs for the treatment of HIV infection are in principle eligible for inclusion in List 1B of the Health Insurance Regulation. These products do not require a pharmaco-economic evaluation. This means that an assessment of the interchangeability does not apply here.
As long as the Ministry maintains the separate reimbursement policy for HIV-inhibiting medicinal products, the National Health Care Institute will, where appropriate, prepare a summary report in the form of a letter report when assessing an HIV inhibitor for inclusion in the GVS (i.e. for placement on List 1B of the Health Insurance Regulation).

Guiding principles of the assessment
Per tablet, Rukobia® contains 600mg fostemsavir, an antiretroviral drug with a new mechanism of action compared to current HIV-inhibiting medicinal products. Fostemsavir is an attachment inhibitor from a new therapeutic class.

Rukobia®/fostemsavir, in combination with other antiretrovirals, is indicated for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.[1] [2]
The recommended dose is 600 mg twice a day.

The marketing authorisation holder claims that this medicinal product, in combination with other antiretroviral drugs, has a therapeutic added value for the treatment of adults for whom it is otherwise not possible to construct a suppressive anti-viral regimen. The application is related to the placement of Rukobia® on List 1B of the Health Insurance Regulation.

Treatment of HIV-1 infection in therapy-experienced patients [3] [4] [5]
The treatment of HIV with a combination of antiretroviral therapy (cART) is aimed at maximum and long-term virological suppression with recovery and preservation of immune functions and prevention of virus transmission. In the long term, it aims to prevent the progression of the disease into AIDS and AIDS-related morbidity and mortality.
In case of insufficient effect of cART, despite good patient compliance, the therapy is adapted on the basis of resistance . In the event of virological failure, it is recommended to construct a new cART as soon as possible, preferably consisting of three active substances. Because of the risk of resistance, adding one new active substance to a failing regime is not recommended. Caution in cART adjustment is desirable if only one new active substance is available and there is no clinical disease progression, and when the CD4+ count is > 200 cells/mm³.

The treatment guideline names fostemsavir and ibalizumab (ibalizumab is not yet available in the Netherlands) as options for patients with chronic viremia who do not have sufficient treatment options to construct a fully suppressive cART.[4]

Substantive assessment
The results of the BRIGHTE study are available to support the therapeutic value of fostemsavir for heavily treatment-experienced HIV-1 patients.[6] [7]

In a multi-centre phase 3 study, 371 heavily ART-experienced participants who had multi-resistant HIV-1 and had experienced virological failure were studied. The participants were divided into two cohorts, based on their remaining treatment options.

- The randomised cohort (n=272) included patients with at least one fully active, approved ART drug in at least one but not more than two classes. These patients were randomised for fostemsavir (oral; 600 mg twice daily) or placebo for 8 days, followed by open-label fostemsavir plus optimised background therapy.
- In the non-randomised cohort (n=99), participants without remaining ART options were started on open-label fostemsavir (oral; 600 mg twice daily) plus optimised background therapy on day 1.

The primary endpoint for the randomised cohort was a change in *viral loa*d on day 8 compared to the baseline. In the fostemsavir group, the average reduction in *viral load was* 0.79±0.05 $\log_{10}$ copies/ml versus 0.17±0.008 $\log_{10}$ copies/ml in the placebo group (P<0.001).
In week 96 (all treated with fostemsavir), 60% of participants in the randomised cohort and 37% of those in the non-randomised cohort had *a viral load* of <40 copies/ml, with an average CD4 increase of 205 cells/mm^3 and 119 cells/mm^3, respectively.
In the randomised cohort, the percentages of virological suppression (HIV-1 RNA <40 copies per ml) increased from 53% (144/272) in week 24 to 60% (163/272) in week 96. Response rates in the non-randomised cohort were 37% (37/99) in week 24 and week 96.

The average increase in CD4 cells from baseline to week 96 was 205 cells/L (SD 191) in the randomised cohort and 119 cells/µL (SD 202) in the non-randomised cohort.

In a number of cases (26/371; 7%), side effects led to cessation of treatment. 12/272 (4%) of people in the randomised cohort and 17/99 (17%) in the non-randomised cohort died; the median baseline CD4 count for participants who died was 11 cells per µl.
The most severe side effect was the immune reactivation syndrome (frequency 1%-10%).[1] The most frequently observed side effects during treatment were diarrhoea (24%), headache (17%), nausea (15%), rash (12%), abdominal pain (12%) and vomiting (11%).

Based on the above, we can conclude that fostemsavir, in combination with other antiretroviral drugs, has a therapeutic added value for the treatment of adults with a multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen.

FK advice
Fostemsavir has no place in the treatment of therapy-naive adults with HIV-1, but can be applied in heavily treatment experienced adults. Antiretroviral therapy in therapy-experienced patients with HIV-1 infection is strongly focused on the individual. The basic principle of a switch to another combination treatment is to restore or maintain virus suppression without (overly) jeopardizing future treatment options.
Fostemsavir, in combination with other antiretroviral drugs, can be applied for the treatment of adults with a multi-drug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen.

BIA
It is expected that 33 patients will be eligible for fostemsavir. This number has been suggested in an advisory board with clinical experts (organised by the marketing authorisation holder), in which they indicated that on average 0 to 5 patients per large treatment centre and on average 1 patient per small treatment centre are eligible. With 6 large treatment centres and 18 smaller treatment centres, the total number of patients is 33 (((0+5)/2*6)+18).
A 100% market penetration is assumed. Most patients will likely not have another antiretroviral drug substituted. Based on the pharmacy purchasing price per tablet (600 mg) of €51.67, an intake of 2 tablets per day and a lifetime treatment period, the total cost per patient per year is €37,719 (51.67*2*365). As a result, the addition of fostemsavir to the GVS will result in a budget impact of €1.2 million.

Advice from the National Health Care Institute

Rukobia® (fostemsavir) can be included in the GVS on List 1B and List 2 of the Health Insurance Regulation.

For all antiretroviral drugs, condition 8 applies:

- Only for an insured person who has a medical indication for treatment with such a medicinal product for which the medicinal product is registered under the Medicines Act, provided that this medicinal product does not belong to the insured benefits if it is used as a pre-exposition prophylaxis to reduce the risk of infection with the human immunodeficiency virus.

In addition, we recommend the following additional condition for fostemsavir:

- Only for an insured person with a multi-drug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

National Health Care Institute
Care
Medicinal Products

Date
29 November 2021

Our reference
2021042172

[1] EMA Amsterdam 2021. SmPC Rukobia®. Consulted in November 2021 via https://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:3::SEARCH:::P0_DOMAIN,P0_LANG,P3_RVG1:H,NL,126217

[2] EMA Amsterdam 2021. EPAR Rukobia®, consulted in November 2021 via https://www.ema.europa.eu/en/medicines/human/EPAR/rukobia

[3] NVHB. Guideline HIV treatment Dutch Association of HIV Practitioners. 2021.

[4] DHHS. HIV treatment clinical guidelines by the Department of Health and Human Services (DHHS) of the United states. 2021. Consulted in November 2021 via https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/virologic-failure?view=full

[5] FK. (https://www.farmacotherapeutischkompas.nl/bladeren/indicatieteksten/hiv_infectie)

[6] Kozal M, Aberg J, Pialoux G, et al. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection. The New England Journal of Medicine. 2020;382(13):1232-43. Supplement included.

[7] Lataillade M, Lalezari JP, Kozal M, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. The Lancet HIV. 2020;7(11):e740-e51. Supplement included.