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2022030938

Date 22 September 2022
Subject GVS Assessment lenacapavir (Sunlenca®)

Case number
2022012865

Our reference
2022030938

Your reference
CIBG-22-04193

Your letter of
2 August 2022

Dear Mr Kuipers,

In your letter of 2 August 2022 (CIBG-22-04193), you asked the National Health Care Institute to assess whether the medicinal product lenacapavir (Sunlenca®; film-coated tablet and solution for injection) can be included in the Medicine Reimbursement System (GVS). Lenacapavir has been evaluated via the parallel procedure.[1]

Therapeutic indication Sunlenca®:[2]
Lenacapavir, in combination with other antiretroviral(s), is i indicated for the treatment of adults with a multi-drug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.

The marketing authorisation holder is asking for this medicinal product to be included in List 1B of the Health Insurance Regulation.

Guiding principles of the assessment

CBG-ZIN parallel procedure
A parallel procedure means that the reimbursement process is started while the registration process has not yet been completed. Medicinal products that go through these parallel procedures, rather than the current sequential procedures, will become available to the patient more quickly. The EMA registration of lenacapavir (Sunlenca®) was published on the EMA website on 25 August 2022. This is normally the time when a reimbursement dossier can be submitted. Due to the parallel procedure, the National Health Care Institute can now quickly advise on the reimbursement after registration.

Reimbursement policy for HIV-inhibiting medicinal products
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

[1] National Health Care Institute, Diemen. CBG-ZIN parallel procedure. To be consulted via: https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-van-geneesmiddelen/parallelle-procedure

[2] EMA Amsterdam 2022. SmPC Sunlenca. Consulted on 1 September 2022 via https://www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_nl.pdf

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Health Insurance Regulation (Rzv). These products do not require a pharmaco-economic evaluation. This means that an assessment of the interchangeability does not apply here.

At the consultation, the occupational group once again raised the question of whether the special reimbursement policy for HIV-inhibiting medicinal products should be reconsidered. The National Health Care Institute shares this view. In view of developments in HIV-inhibiting medicinal products, the need for a separate reimbursement policy in 2022 is less obvious than in 2000. In our 2011 report on HIV-inhibiting medicinal products, the National Health Care Institute already explored a number of options.[3] Once again, I would like to ask you to reconsider the separate reimbursement policy for HIV-inhibiting medicinal products.

Lenacapavir (Sunlenca®) [2] [4]
Lenacapavir is an HIV-inhibiting medicinal product with a new mechanism of action. It is a selective inhibitor of the HIV-1 capsid function. Treatment with this product leads to malformed viral capsids.
Lenacapavir is available as solution for subcutaneous injection. Film-coated tablets are available for the initial phase.
Each 1.5 ml injection vial contains lenacapavir sodium equivalent to 464 mg lenacapavir. A pack contains 2 vials.
Each film-coated tablet contains lenacapavir sodium, equivalent to 300 mg of lenacapavir. A package contains 5 film-coated tablets, sufficient for initial treatment.

Recommended dose for initial phase: on day 1 and day 2 once a day 600 mg of lenacapavir orally and on day 8, 300 mg (*oral lead-in*); on day 15 subcutaneous injection of lenacapavir (927 mg as 2 injections of 1.5 ml administered at two different sites in the abdomen).
Recommended dose for maintenance phase: subcutaneous injection of lenacapavir (927 mg lenacapavir via 2 injections of 1.5 ml), administered once every 6 months (26 weeks) from the date of the last injection (±2 weeks).

Note: lenacapavir is not registered as a monotherapy. This product should only be used in combination with other antiretrovirals (optimised background treatment).

Substantive assessment
The marketing authorisation holder claims that lenacapavir, for the registered indication, has a therapeutic added value compared to placebo. Furthermore, the marketing authorisation holder claims that lenacapavir has a therapeuticvalue comparable with fostemsavir (Rukobia®). The National Health Care Institute issued a GVS advisory report on fostemsavir in 2021.[5]
To substantiate the desirable and undesirable effects of lenacapavir in adults with multi-resistant HIV-1 infection, the marketing authorisation holder has provided

[3] National Health Care Institute. Diemen. 2011. Report on HIV-inhibiting medicinal products. To be consulted via https://www.zorginstituutnederland.nl/publicaties/rapport/2011/05/30/signalement-hiv-remmende-geneesmiddelen

[4] EMA Amsterdam 2022. EPAR Sunlenca. Consulted on 1 September 2022 via https://www.ema.europa.eu/en/medicines/human/EPAR/sunlenca

[5] National Health Care Institute Diemen 2021. GVS advisory report fostemsavir (Rukobia®) for HIV-1 infection. To be consulted via https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/12/01/gvs-advies-fostemsavir-rukobia-bij-hiv-1-infectie

data from the pivotal clinical study, the CAPELLA study.[6] Additional data on this study, as included in the EPAR, is also part of this dossier.[4]

The CAPELLA study is a partially randomized, placebo-controlled multicentre study with a total of 72 patients (divided into two cohorts) with multi-resistant HIV-1 infection.

The inclusion criteria of this phase 3 study are as follows:
- 12 years or older with a body weight of ≥35 kg,
- receiving a stable, failing drug therapy (as indicated by an HIV-1 RNA level ≥ 400 copies per millilitre) for at least 8 weeks,
- with documented resistance to at least two antiretroviral drugs from at least three of the four main classes (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and integrase inhibitors),
- no more than two fully active antiretroviral drugs from the four main classes that could be effectively combined.

Cohort 1: patients were randomized into the oral lenacapavir (n=24) or placebo (n=12) group. The intervention group was treated with lenacapavir tablets (on days 1/2/8 with 600/600/300 mg per day) and the control group with placebo tablets (*oral lead-in*). In addition to the study medication, all patients still used their existing, failing therapy for 14 days; in the study this is also called functional monotherapy.
During the maintenance period, starting on day 15, patients in the lenacapavir group were given subcutaneous lenacapavir once every 6 months. Patients from the placebo group started on day 15 with lenacapavir tablets (*oral lead-in*), followed by subcutaneous lenacapavir. During the treatment with lenacapavir injections, all patients received optimized background therapy.
Cohort 2: all patients (n=36) received open-label oral lenacapavir (*oral lead-in*) with optimized background therapy; subcutaneous lenacapavir was then administered once every 6 months from day 15.

The primary endpoint of the study was the percentage of patients in cohort 1 who had a reduction from baseline of at least 0.5 $\log_{10}$ copies per millilitre in the plasma HIV-1 RNA viral load at the end of *the oral lead-in* (day 15). An important secondary endpoint was the percentage of patients in cohort 1 with an HIV-1 RNA of < 50 copies per millilitre at week 26 and week 52.

Clinical study outcomes
In total, 72 patients (median age: 52 years) were studied in the CAPELLA study, of which 36 in cohort 1 (lenacapavir n=24; placebo n=12).[6]
In cohort 1, a decrease of at least 0.5 $\log_{10}$ copies per millilitre of plasma HIV-1 RNA was observed on day 15 in 21 of the 24 patients (88%) in the lenacapavir group, and in 2 of the 12 patients (17%) in the placebo group (absolute difference: 71 percentage points; 95% confidence interval: 35 to 90; P<0.001).[6]
In week 26, a plasma HIV-1 RNA of less than 50 copies per millilitre was reported in 29 of the 36 patients (81%) of cohort 1 (95% CI: 64-92). In cohort 2, this was the case with 83% of patients.

[6] Segal-Maurer S, DeJesus E, Stellbrink HJ, et al. Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection. N Engl J Med. 2022 May 12;386(19):1793-1803. Plus supplementary appendix.

Results at week 52 (see EPAR) shows a similar measure of viral suppression.[4]

In total, 19 of the 72 patients (11 in cohort 1 and 8 in cohort 2) showed drug resistance and they were then studied for the emergence of resistance to capsid inhibitor. During the maintenance period, 8 of the 19 patients with resistance (4 in cohort 1 [1 in the lenacapavir group and 3 in the placebo group] and 4 in cohort 2) developed lenacapavir-associated capsid substitutions.[6]

The most common side effects of lenacapavir in heavily pre-treated adult patients with HIV were injection site reactions (63%) and nausea (4%).[2]

Discussion
In the CAPELLA study, 47% of patients in cohort 1 (n=36) reported resistance to all four major classes of antiretroviral medication. In addition, many of the patients were treated with the group of integrase inhibitors (54%) and protease inhibitors (42%), while other patients had resistance to products recently approved for heavily treated adults (ibalizumab in 11 of 33 patients [33%] and fostemsavir in 10 of 33 [30%]).[5] Of the 36 subjects, 6 patients (17%) no longer had a fully active antiretroviral agent in their optimised background regimen.
After the *oral lead-in* phase with tablets (day 15), 21/24 (88%) patients from the lenacapavir group reached the primary target, i.e. a reduction of at least 0.5 $\log_{10}$ copies per millilitre in HIV-1 RNA. In the placebo group, this was the case for 2/12 (17%) patients. A statistically significant difference of 71% has been measured between these two groups.
Thus: In adult patients with multi-resistant HIV-1 infection who have experienced virological failure, adding lenacapavir to the treatment has proven effective compared to placebo. Lenacapavir thereby has a therapeutic added value compared to placebo.

In addition to a direct comparison with placebo, the marketing authorisation holder has also tried to make an indirect comparison between lenacapavir and fostemsavir. Since the treatment of patients with multi-resistant HIV-1 infection is highly individual, a comparison, indirect or otherwise, between these two products is difficult. The patient characteristics are diverse in nature and the number of remaining treatment options varies for each individual. The available study data from lenacapavir are limited. For example, the CAPELLA study contains data from only 72 patients who have not been treated more than twice with a subcutaneous injection of lenacapavir.
In addition, the outcome measurements differ between the CAPELLA study (lenacapavir) and the BRIGHTE study (fostemsavir), such as a plasma HIV-1 RNA of <50 copies/ml versus a plasma HIV-1 RNA of <40 copies/ml. This makes an indirect comparison difficult. Both products have proven to be effective compared to placebo in the target patient population of adults with multi-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen. Due to the absence of a direct comparative study of lenacapavir and fostemsavir, it is not possible to make a valid statement about the therapeutic evaluation between these two substances.

Finally
- Although the subcutaneous administration of lenacapavir is once every 6 months, compliance with therapy is still an important issue. The daily use of the background treatment, apart from lenacapavir, remains crucial.

- For the proper use of lenacapavir, the treating physician has an important role, for example applying the correct start and stop criteria.
- Lenacapavir is not indicated for the treatment of therapy-naïve patients with HIV-1, HIV-2 infection, or as pre-exposure prophylaxis or as a combination treatment with fostemsavir. The effectiveness of these applications has not been demonstrated.

On the basis of the above, it can be concluded that lenacapavir meets the established medical science and medical practice.

FK advice
Lenacapavir has no place in the treatment of therapy-naive adults with HIV-1, but can be applied for previously heavily treated adults. Antiretroviral therapy in previously treated (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 the virus suppression without (overly) jeopardizing future treatment options.
Lenacapavir, 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 antiviral regimen.

Budget impact analysis (BIA)
It is expected that 33 patients will be eligible for lenacapavir or fostemsavir. This number was already estimated in the BIA for fostemsavir at the end of 2021 and this still applies. The clinical expert group consulted at that time in 2021 indicated that an average of 0 to 5 patients per large treatment centre and an average of 1 patient per small treatment centre were eligible. With 6 large treatment centres and 18 small treatment centres in the Netherlands, the total number of patients is 33 (((0+5)/2*6)+18). The marketing authorisation holder for lenacapavir has had an additional analysis done by Stichting HIV Monitoring (SHM); this has identified 26 patients who would be eligible for fostemsavir or lenacapavir. SHM indicated that this may be a small underestimation and the clinical experts consulted by the marketing authorisation holder also indicated that 26-33 patients is a realistic number. Patients usually join mid-year (in year 1, 50% of the total cost per year). It is assumed that the market penetration of medicinal products with a new mechanism of action (lenacapavir or fostemsavir) is 50% in the first year, 75% in the second year and 85% in the third year. Lenacapavir's market share is then 80% and fostemsavir 20% in the base case, and 90% versus 10% in a maximum scenario. In a situation without lenacapavir, all patients with multi-resistant HIV-1 infection for whom the physician decides to use another HIV inhibitor with a new mechanism of action would receive fostemsavir. Lenacapavir therefore substitutes for fostemsavir.
Based on the pharmacy purchase price (AIP) of lenacapavir of €3,143 per pack of 5 tablets 300 mg and €18,858 per pack of 2 vials of 1.5 ml with 464 mg lenacapavir, the costs per patient in the first year are €40,859 (5 tablets of 300 mg plus 4 vials of 1.5 ml) and in subsequent years €37,716 (4 vials of 1.5 ml per year). The total costs of fostemsavir are, based on the purchase price per tablet (600 mg) of €51.67, a daily intake of 2 tablets and a lifetime treatment period, €37,719 (51.67*2*365) per patient per year. Because the costs per patient per year of lenacapavir and fostemsavir are almost the same, the budget impact from the admission of lenacapavir is negligible.
This BIA does not take into consideration any future combination of treatment

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with both medicinal products. These are only medication costs; this does not take into account any additional healthcare costs outside the pharmaceutical budget. Lenacapavir must be administered subcutaneously and therefore requires a medical procedure. These costs – even though they are probably limited in relation to the total costs – have not been taken into consideration.

Advice from the National Health Care Institute
Lenacapavir (Sunlenca®) can be included on List 1B and List 2 of the Health Insurance Regulation.
The further conditions set out in List 2 may be worded as follows.

139. Fostemsavir, lenacapavir
Condition:
Only for an insured person

a) with a multi-drug resistant human immunodeficiency virus-1 (HIV-1) infection who cannot otherwise be treated with a suppressive antiviral regimen, and
b)
c) who does not use a combination of fostemsavir with lenacapavir, and
d) who does not use this medicinal product as a pre-exposure prophylaxis to reduce the risk of infection with the human immunodeficiency virus.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board