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Minister of Health, Welfare and Sport
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2022024289

Date 4 July 2022
Subject Medicine Reimbursement System advisory report on cannabidiol (Epidyolex®)

National Health Care Institute

Care
Medicinal products

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Our reference

2022024289

Dear Mr Kuipers,

In this letter, the National Health Care Institute makes recommendations about cannabidiol (Epidyolex®) as adjuvant treatment in patients aged 2 years and older with therapy-resistant Lennox-Gastaut syndrome (LGS) or therapy-resistant Dravet syndrome (DS).

The reason for this advisory report is your request of 12 October 2021 (CIBG-21-02629) for a substantive review to determine whether cannabidiol is interchangeable with another medicinal product included in the Medicine Reimbursement System (GVS).

Cannabidiol can be placed on List 1B. The National Health Care Institute concludes that adding cannabidiol combined with clobazam to the standard treatment has added value compared to the standard treatment alone. There is still uncertainty about the long-term effects. In addition, there is uncertainty about the cost-effectiveness. In addition to the uncertainty as investigated in a more realistic scenario analysis, considerable uncertainty about the utility values plays a role. That is why the National Health Care Institute is recommending a price reduction of at least 20%. The indication expansions that are expected in the short term should also be included in the price negotiations. The National Health Care Institute recommends using price bands in the price negotiation for increases in volume. The Insured Package Advisory Committee (ACP) believes that the above-mentioned price reduction alone is insufficient to reach a socially responsible price. The committee thinks that the uncertainty about the cost-effectiveness as a result of the uncertainty about the utility values is considerable. That is why the committee believes that an amount below the reference value of 80,000 euros per QALY is appropriate. For that reason, the committee believes a price reduction of at least 25% to be suitable.

I would like to explain our findings and final conclusion below.

General

At your request, the National Health Care Institute assesses whether new care should be part of the health insurance package, working from the perspective of

the basic health insurance package paid from joint premiums. To be able to make a recommendation, the National Health Care Institute has assessed cannabidiol on the basis of the four package criteria¹: effectiveness², cost-effectiveness³, necessity and feasibility. We consider these both in the scientific sense and in terms of public support. We also review the aspects of efficiency and transparency. The National Health Care Institute is advised in its package reviews by two independent committees:

- the Scientific Advisory Board (WAR) for the review of data according to established medical science and medical practice, and to determine cost-effectiveness; and
 - the Insured Package Advisory Committee (ACP) for the social deliberations.
- We also consulted stakeholders during the assessment process.

Cannabidiol (Epidyolex®)

Cannabidiol is indicated for use as adjuvant therapy in combination with clobazam for the seizures that are associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients aged 2 years and older.

The request for reimbursement is related to patients with *refractory* LGS or DS in whom insufficient seizure control has been achieved with the currently available treatments. Therapy resistance is defined here as achieving insufficient seizure control with at least two anti-epileptics.

Comprehensive weighting of package criteria

Established medical science and medical practice

For patients with LGS, a subgroup analysis of 2 RCTs has shown that cannabidiol in combination with clobazam is likely to have a clinically relevant effect on the number of patients with LGS who experience a reduction of 50% or more in the frequency of drop attacks. On average, there was a decrease of 43% in the number of drop attacks compared to a placebo. Additionally, cannabidiol in combination with clobazam probably has a clinically relevant effect on the number of patients with LGS whose S/CGIC score improves (*subject/caregiver global impression of change*), which is also seen as a crucial patient/caregiver-reported outcome measure.

For patients with DS, a subgroup analysis of 2 RCTs has shown that cannabidiol in combination with clobazam results in a statistically significant effect on the number of patients in whom the frequency of convulsions decreases by 50% or more. On average, there was a decrease of 37% in the number of convulsions compared to a placebo. Additionally, cannabidiol in combination with clobazam probably has a clinically relevant effect on the number of patients with DS whose S/CGIC score improves.

Cannabidiol in combination with clobazam complies with established medical science and medical practice as adjuvant treatment for therapy-resistant patients aged 2 years and older with LGS or DS. Based on the available data, the National Health Care Institute concludes that adding cannabidiol combined with clobazam

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¹ *Real-world package management 3* (2013). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

² *Established medical science and medical practice assessment: updated version* (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

³ *Cost-effectiveness report* (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

to the standard treatment has added value compared to the standard treatment alone.

Budget impact analysis

The macro-level costs are €33.4 million at a dosage of 12 mg/kg per day or €55.6 million at a dosage of 20 mg/kg per day in the third year after inclusion in the basic health care package. In the third year, 1135 patients are eligible for treatment with cannabidiol (Epidyolex®).

Cost-effectiveness

The cost-effectiveness analyses provided are of sufficiently high methodological quality. For patients with LGS, the ICER is €70,561 per QALY compared to placebo, which is cost-effective at a reference value of €80,000 per QALY. The likelihood that cannabidiol combined with clobazam is cost-effective compared to a placebo combined with clobazam is 59.34%.

For patients with DS, the ICER is €37,584 per QALY compared to placebo, which is cost-effective at a reference value of €80,000 per QALY. The likelihood that cannabidiol combined with clobazam is cost-effective compared to a placebo combined with clobazam is 76.85%.

However, both outcomes are based on an unrealistic, long-term extrapolation of the treatment effect. Based on a scenario where less optimistic assumptions are made about extrapolating the treatment effect, the ICER for LGS increases to €108,877 per QALY and to €109,769 per QALY for DS. Based on these scenarios, the price of cannabidiol would have to decrease by 20% for it to fall below the reference value of €80,000 per QALY.

Final conclusion

Cannabidiol can be placed on List 1B. The National Health Care Institute concludes that adding cannabidiol combined with clobazam to the standard treatment has added value compared to the standard treatment alone. There is still some uncertainty about the long-term effects. In addition, there is uncertainty about the cost-effectiveness. In addition to the uncertainty as investigated in a more realistic scenario analysis, considerable uncertainty about the utility values plays a role. That is why the National Health Care Institute is recommending a price reduction of at least 20%. The indication expansions that are expected in the short term should also be included in the price negotiation. The National Health Care Institute recommends using price bands in the price negotiation for increases in volume. The Insured Package Advisory Committee (ACP) believes that the above-mentioned price reduction alone is insufficient to come to a socially responsible price. The committee thinks that the uncertainty about the cost-effectiveness as a result of the uncertainty about the utility values is considerable. That is why the committee believes that an amount below the reference value of 80,000 euros per QALY is appropriate. For that reason, the committee believes a price reduction of at least 25% to be suitable.

If treatment with cannabidiol (Epidyolex®) is included in the basic health care package after a successful price negotiation, the National Health Care Institute recommends the following reimbursement condition:

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Conditions for cannabidiol

Exclusively for an insured person who uses cannabidiol as adjuvant therapy in combination with clobazam in seizures that are associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients aged 2 years and older. The treatment must be discontinued if the seizure frequency has not decreased by at least 30% after 6 months at the maintenance dosage.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

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