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Our reference
2025001880

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Date 24 February 2025
Re: GVS advice extension of further condition for cannabidiol (Epidyolex®) in tuberous sclerosis complex (TSC)

Dear Ms Agema,

In this letter, the National Health Care Institute advises you on the extension of the additional conditions for reimbursement of cannabidiol (Epidyolex®) as an additional treatment for therapy-resistant seizures in patients with tuberous sclerosis complex (TSC) in the Medicine Reimbursement System (GVS). This advice was prompted by your request in the letter of 24 June 2024 (CIBG-24-07072).

TSC is a rare hereditary disorder in which certain cells can grow uncontrollably. This causes benign tumours in various areas of the body, such as the kidneys, skin or brain. These tumours can lead to various symptoms. In the brain, these tumours often lead to seizures, intellectual disabilities and behavioural problems. TSC cannot be cured. For patients with epileptic seizures due to TSC, several medicinal products are available that can prevent seizures. They may also undergo surgery or follow a special (ketogenic) diet.

Recorded indications
Cannabidiol (Epidyolex®) is indicated for use as an adjuvant treatment for seizures associated with tuberous sclerosis complex (TSC) in patients aged 2 years and older. In addition, cannabidiol is indicated (and already being reimbursed) for adjuvant treatment in seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in combination with clobazam in patients aged 2 years and older.

Cannabidiol is already listed in the GVS on List 1B for the LGS and DS indications with the following additional conditions in List 2.

Current condition cannabidiol
Only for insured persons aged two years and over who use this medicinal product as adjuvant therapy for seizures associated with Lennox-Gastaut Syndrome (LGS) or Dravet syndrome (DS). The treatment must be discontinued if the seizure frequency has not decreased by at least 30% after 6 months on the maintenance dosage.

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Claim by the marketing authorisation holder
The MAH claims an added value for cannabidiol when added to standard treatment compared to the best supportive care for therapy-resistant TSC-related seizures in patients aged 2 years and older. Therapy resistance is defined as achieving insufficient seizure control with at least two anti-epileptic agents.

Advice

The National Health Care Institute advises you to adjust the additional conditions of cannabidiol (Epidyolex®) as stated below. This new condition applies only to cannabidiol and not to fenfluramine.
New condition cannabidiol

> Only for an insured person aged two years and older who uses this medicinal product as adjuvant therapy in seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) or in treatment-resistant seizures associated with tuberous sclerosis complex (TSC). Treatment should be discontinued if, after 6 months on a maintenance dose, the seizure frequency has not decreased at least 30% when evaluated according to the guidelines accepted by the relevant professional associations in the Netherlands.

I will explain the preparation of this advisory report below.

Substantive assessment
Therapeutic value
The National Health Care Institute, advised by the Scientific Advisory Board (WAR), has concluded that the addition of cannabidiol to the standard treatment for the said indication has a therapeutic added value compared to standard treatment alone.

For patients with TSC, the analysis of a randomised controlled trial (RCT) indicates that the addition of cannabidiol to standard treatment may have a clinically relevant effect on the number of patients experiencing a ≥50% decrease in seizure frequency. Improvement in quality of life has been reported in the majority of patients. Patients treated with cannabidiol may experience side effects. Because some patients experience insufficient benefit from treatment with cannabidiol, it is important that in daily practice, the effectiveness is assessed every six months for 2 years and that treatment is stopped if insufficient effect is observed.

Budget-impact analysis
Depending on the number of patients who will discontinue treatment in practice, the National Health Care Institute estimates that 359 to 422 patients per year will be treated with cannabidiol for this indication in year 3 after inclusion in the health insurance package.
There is also uncertainty about the dose that patients will receive. Taking into account these uncertainties, this results in a budget impact of €8.8 to 17.0 million in the third year.

Cost-effectiveness
The National Health Care Institute concluded that the cost-effectiveness analysis of the MAH is of sufficient quality. The cost-effectiveness estimate at 15 mg/kg/day is below the reference value of €80,000 per QALY considered relevant for this condition. However, if practical use shows that the maximum

recommended dose is administered, the cost-effectiveness estimate will exceed the reference value, since the deterministic ICER is €52,039/QALY at a dose of 15 mg/kg/day and €139,664/QALY at 25 mg/kg/day. If the applied dose in daily practice is closer to 25 than 15 mg/kg/day, a reference value of €80,000 would require the price of cannabidiol to be reduced by about 30% to be cost-effective. Since the dose of 15 mg/kg/day is currently estimated as the most realistic scenario, based on the information of the professional association, cannabidiol is likely to be a cost-effective intervention. In addition to uncertainty about dosing in daily practice, there is also uncertainty about the percentage of patients who discontinue treatment due to insufficient treatment effect, long-term treatment effects, the gains in quality of life and productivity gains. Only the dose uncertainty is included in the ICER range. Should the number of patients who discontinue due to insufficient treatment effect turn out to be lower than expected, there is a possibility to reassess. Due to the uncertainty about the dosage and the percentage who discontinue due to insufficient treatment effect, the actual price for cannabidiol for TSC patients should not exceed the current negotiated price for DS and LGS.

Should you need any further information, please do not hesitate to contact us. The assessment reports have been added as annexes (pharmacotherapeutic report, budget-impact analysis and pharmaco-economic report).

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board

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