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Our reference
2021002032

Date 2 February 2021
Subject GVS advice givosiran (Givlaari®)

Dear Ms van Ark,

In this letter, the National Health Care Institute advises you about givosiran (Givlaari®).

In your letter of 7 September 2020 (CIBG-20-0910), you requested the National Health Care Institute to assess whether the product givosiran 189 mg (Givlaari®) is interchangeable with another product that is included in the Medicine Reimbursement System (GVS).

The National Health Care Institute has concluded that givosiran is not interchangeable with another product included in the GVS. Givosiran has a therapeutic added value compared to the standard treatment (best supportive care). However, there are uncertainties regarding long-term complications and optimal dosage. In addition, the costs per patient are very high. In view of the above, the estimated cost-effectiveness is highly unfavourable.

The National Health Care Institute advises you to include givosiran on List 1B of the GVS, provided that the conditions of a substantial price reduction are met and agreements are made for appropriate use and evaluation of the effectiveness and safety in the long term .

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

General
From the point of view of the basic package paid from joint premiums, the National Health Care Institute makes its assessment of whether new care should be part of the insured package. We take into consideration the degree of certainty that this will be achieved, both in the scientific sense, as well as in terms of public support, and we consider the efficiency and transparency aspects. The National Health Care Institute is advised by two independent committees: the Scientific Advisory Board (WAR) for the assessment of the established medical science and medical practice criterion and the determination of the cost-effectiveness, and the Insured Package Advisory Committee (ACP) for the social assessment. We also consulted stakeholders during the assessment process.
The National Health Care Institute assessed givosiran on the basis of the four

package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility.

Registered indication
Givosiran (Givlaari®) is indicated for the treatment of acute hepatic porphyria (AHP) in adults and adolescents who are 12 years and older.
Each ml of solution contains givosiran sodium equivalent to 189 mg of givosiran. Each vial contains 189 mg of givosiran. Givosiran has an orphan drug status.

The recommended dosage of givosiran is 2.5 mg/kg, administered once a month by subcutaneous injection. The dosage is based on the actual body weight.

The marketing authorisation holder has requested reimbursement for a specific group within the registered indication:
For the treatment of acute hepatic porphyria in patients with a confirmed diagnosis of acute hepatic porphyria and a recent history of frequent acute porphyria attacks (≥2 acute attacks over 6 months or on hemin prophylaxis).

Review of interchangeability
To determine the place of a medicinal product in the GVS, the product's interchangeability with medicinal products already included in the GVS must first be assessed.
Givosiran (Givlaari®) is not interchangeable with any products in the GVS.

Therapeutic value
Givosiran has been studied as an addition to the best supportive care in a randomized, double-blind, placebo-controlled phase 3 study (ENVISION). The study consists of a 6-month double-blind period and an open-label extension period (up to 29 months). The open-label extension study has not yet been completed. At the time of the assessment, data were available on a median givosiran treatment duration of 17 months.

Compared to best supportive care, givosiran results in a clinically relevant decrease in the number of acute porphyria attacks requiring urgent medical assistance.
The average number of acute porphyria attacks in the ENVISION study requiring acute medical assistance was three per year in the givosiran group versus thirteen per year in the placebo group (both as an addition to best supportive care). Halving the number of attacks in the proposed population is considered clinically relevant by the professional group.

An acute porphyria attack is accompanied by severe pain and has a significant negative impact on the daily functioning of a patient with acute hepatic porphyria. The decrease in the number of acute porphyria attacks due to treatment with givosiran is a possible explanation for the observed decrease in pain and the positive effect of givosiran on various aspects of quality of life. Whether there is a significant reduction in pain between the attacks has not been demonstrated. In addition, no effect of givosiran on other chronic symptoms, such as fatigue and

[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

nausea, has been demonstrated.

There is no evidence for a beneficial effect of givosiran on (preventing) long-term complications such as kidney disease and liver disease. On the basis of the undesirable effects data, increased transaminase values have been observed more frequently during treatment with givosiran. In addition, progression of renal impairment has been observed in some patients with already existing renal disease. Monthly liver function tests in the first 6 months of treatment and checks of the renal function in patients with existing kidney disease have been indicated.

The open-label extension study looked into the effect of givosiran, both in the recommended dosage of 2.5 mg/kg/month, and in a lower dose of 1.25mg/kg/month.
However, the difference in effect between the different doses is difficult to interpret. This is because of the non-randomized assignment to the different dosage groups, the small number of patients with limited follow-up duration and the lack of a parallel control group. Further research into the effect of the different dosages is recommended.

Budget impact analysis
Each vial contains 1 ml of injection solution with 189 mg of givosiran per ml. The pharmacy purchase price (AIP) of givosiran is €46,026.85 per vial. The average annual cost of prophylactic treatment with givosiran is €552,322.20 per patient.

Inclusion of givosiran for the indicated indication will result in €8 to €11 million per year. This is based on an estimate of 15-21 patients in the third year who will be treated with givosiran.

Pharmaco-economic analysis
The cost-effectiveness analysis provided by the marketing authorisation holder was of sufficient quality. The analysis shows an incremental cost-effectiveness ratio (ICER) of €199,836 per QALY, compared to best supportive care. The probability that givosiran is cost-effective compared to best supportive care is about 0% at a reference value of €50,000 per QALY. If an ICER of €199,836 per QALY is assumed, the price of givosiran (on average €552,322.20 per patient per year) should drop by at least 40% to reach an ICER that falls below the reference value of €50,000 per QALY.

Final conclusion
The National Health Care Institute has concluded that givosiran (Givlaari®) is not interchangeable with another product included in the GVS. Givosiran has a therapeutic added value compared to the standard treatment (best supportive care). The National Health Care Institute recommends that givosiran (Givlaari®) be included in List 1B of the GVS, provided that the following conditions are met:

- A substantial price reduction of givosiran, given the high cost per patient and unfavourable cost-effectiveness.
- Appropriate use criteria for the efficient application of the treatment. The National Health Care Institute is already discussing the making of arrangements for appropriate use with the professional group. In this respect, the National Health Care Institute also recommends that the optimal dosage be assessed, to see whether this can further improve the cost-effectiveness.

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- The monitoring of long-term outcomes to evaluate the effectiveness and safety of givosiran. Regie op Registers is the recommended practice for this. The National Health Care Institute will advise the parties concerned to agree to this practice.

Orphan drugs arrangement
Upon inclusion in the insured package, the National Health Care Institute will conclude an orphan drug arrangement with the parties. This will establish agreements on start-and-stop criteria, an indication committee, data collection and evaluation by means of an (international) register. The first steps have already been taken by the parties. The National Health Care Institute will continue to guide this process. The National Health Care Institute points out that it is important that centres of excellence have sufficient resources to meet the commitments made and to be able to follow the practice properly. The results of the orphan drugs arrangement will be published annually in the Orphan Drugs Monitor in practice.

In the context of the treatment landscape, the National Health Care Institute takes the following points into consideration:
- The initial estimate of the number of patients compared to the actual number treated;
- The cost development compared to the original cost estimate;
- The realisation of an orphan drug arrangement and compliance with this orphan drug arrangement.

If the application of givosiran (Givlaari®) is included in the package after a successful price negotiation, the National Health Care Institute recommends the following compensation conditions:

Condition for givosiran (Givlaari®):
Exclusively for the treatment of acute hepatic porphyria in patients with a confirmed diagnosis of acute hepatic porphyria and a recent history of frequent acute porphyria attacks (≥2 acute attacks over 6 months or on hemin prophylaxis).

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board