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Our reference
2020046256

Date 16 November 2020
Subject Package advice venetoclax (Venclyxto®)

Dear Ms van Ark,

The National Health Care Institute has completed the assessment of venetoclax (Venclyxto®) in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphatic leukaemia (CLL). The reason for this advice was the placing of venetoclax in the package lock for expensive medicinal products.

The National Health Care Institute assessed venetoclax on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. Through this letter, I would like to inform you about the result of the full weighting of these package criteria.
The National Health Care Institute has concluded that, in the above indication, venetoclax (Venclyxto®) meets the legal criterion 'established medical science and medical practice' for two patient groups that fall within the registered indication:

- Non-fit patients with CLL not previously treated and mutated IGHV status, without 17p deletion or TP53 mutation;
- Non-fit patients with CLL not previously treated and *un*mutated IGHV status, without 17p deletion or TP53 mutation.

This is an effective product for these patients, but there are arguments to advise you to negotiate prices and to involve the results of this assessment in your negotiations about ibrutinib.

I will explain the advice below.

General

At your request, the National Health Care Institute assesses whether new care should be part of the insured package. The National Health Care Institute bases its decision on the point of view of the basic health care package paid from joint

[1] 1 Real-world package management 3 (2013). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[2] Current state of science and practice assessment: updated version (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[3] Cost-effectiveness report (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

premiums. The National Health Care Institute is advised by two independent committees: the Scientific Advisory Board (WAR) for the scientific and practical assessment of the data and the determination of the cost-effectiveness, and the Insured Package Advisory Committee (ACP) for the social assessment. The National Health Care Institute has also consulted stakeholders during the assessment process.

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Integral package criteria weighting

Current level of knowledge and practice

Until a treatment is indicated, a wait-and-see policy applies for patients. If treatment is indicated, the choice of therapy in the primary line treatment depends on the patient's fitness, age, and type of mutation. This assessment focusses on non-fit patients with mutated or unmutated IGHV status, without del(17p) or TP53 mutation. Based on the current guideline, venetoclax-obinutuzumab was compared in the assessment with:

1) Chlorambucil-obinutuzumab in patients with mutated IGHV status;
2) Chlorambucil-obinutuzumab and ibrutinib in patients with *un*mutated IGHV status.

Re 1) in this patient population, we conclude that venetoclax-obinutuzumab may lead to greater progression-free survival than chlorambucil-obinutuzumab.
Re 2) we conclude that venetoclax-obinutuzumab is likely to provide a clinically relevant difference in progression-free survival compared to chlorambucil-obinutuzumab in these patients. Because patients in the venetoclax-obinutuzumab study are less fit than patients in the ibrutinib study, we conclude that venetoclax-obinutuzumab possibly leads to a similar progression-free survival as ibrutinib in these patients.
Little is known about: the effect on overall survival (because of the slow progression), the time to the next treatment and the quality of life.
Important identified risks with fatalities in the use of venetoclax (obinutuzumab) are tumour lysis syndrome (TLS), neutropenia and infections. Based on the undesirable effects, no preference can be given to one of the three products.

Budget impact

The National Health Care Institute estimates that approximately 194 patients will be treated with venetoclax-obinutuzumab in the primary line each year. Patients are treated for approximately one year and the total costs per patient per treatment are €84,503. The total costs of treatment with venetoclax-obinutuzumab in the primary line are estimated at €8.2 million per year. The additional costs are €5.6 million when the substitution of the current treatment is taken into account.

Cost-effectiveness

The cost-effectiveness of the two patient groups that meet the established medical science and medical practice has been assessed.
For patients with *un*mutated IGHV status, the National Health Care Institute concludes that the cost-effectiveness analysis of venetoclax-obinutuzumab for the treatment of previously untreated CLL is of sufficient methodological quality. At a reference value of €50,000 per QALY, the treatment with venetoclax-obinutuzumab is cost-effective compared to the treatment with chlorambucil-obinutuzumab. The treatment with venetoclax-obinutuzumab is dominant: the treatment yields more QALYs at lower costs. Including medical expenses in years of life gained does not affect this.

For patients with mutated IGHV status, the National Health Care Institute concludes that the cost-effectiveness analysis of venetoclax-obinutuzumab is of sufficient methodological quality. However, the results of the pharmaco-economic analysis cannot be used for decision-making because there is too much uncertainty about the modelling of the progression-free survival. This is mainly due to the limited availability of data for this particular subgroup. The National Health Care Institute notes that here too the treatment with venetoclax-obinutuzumab seems to be cost saving compared to chlorambucil-obinutuzumab.

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Relationship with other assessment
Ibrutinib monotherapy for the treatment of adult patients with CLL who have not been previously treated, has recently been assessed by the National Health Care Institute. The conclusion was that ibrutinib meets the established medical science and medical practice. Unlike the treatment with venetoclax, which lasts about a year, the treatment with ibrutinib lasts until disease progression, which in most patients is longer than three years. Each year of treatment with ibrutinib costs approximately €70,000.
As the price negotiations have not yet been concluded, ibrutinib has not yet been included in the basic health care package for this indication.

Package advice
Venetoclax is an effective medicinal product for the two patient groups. As far as cost-effectiveness is concerned, there are a number of uncertainties. However, it is certain that the new treatment will reduce costs compared to the current standard treatment.
The National Health Care Institute recommends that venetoclax be admitted to the basic health care package for the patient groups concerned and that the price is negotiated. Two points are important:

- There is already a price negotiation process ongoing for the medicinal product ibrutinib, which is partly an alternative to venetoclax in combination with obinutuzumab. This advice on venetoclax in combination with obinutuzumab should therefore also have repercussions for the ongoing negotiations on ibrutinib;
- Venetoclax is already being reimbursed for several indications. This means that the marketing authorization holder has already been partially compensated for the efforts they have had to make to market the product. This justifies the argument that a lower price can be paid.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board