Venetoclax (Venclyxto®) for the treatment of chronic lymphocytic leukaemia

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated May 8, 2019

Zorginstituut Nederland carried out an assessment in relation to extending the specific conditions for the medicinal product Venetoclax (Venclyxto®) and concluded as follows.

Zorginstituut Nederland has completed its assessment of venetoclax (Venclyxto®) in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one previous treatment. The Minister of Health Welfare and Sport (VWS) placed Venetoclax in the "waiting room" (*sluis*) for expensive medicinal products.

The *Zorginstituut* assessed venetoclax based on the four package criteria[1] effectiveness,[2] cost-effectiveness,[3] necessity and feasibility. Assessing from the perspective of the basic package which is funded from collective premiums, the *Zorginstituut* looks at whether new care is better than what is currently available. We look not only at the degree of certainty that has been realised, from a scientific perspective and from the perspective of societal support, but also at aspects relating to efficiency. The *Zorginstituut* was advised by two independent committees: the Scientific Advisory Board (WAR) which examines data on established medical science and medical practice and determines the cost-effectiveness, and the Insured Package Advisory Committee (ACP) which considers the societal assessment. Stakeholders are also consulted during the process. This letter is to inform the Minister of VWS about the results of our integral assessment of these package criteria.

Integral consideration of the package criteria and package advice

Venetoclax in combination with rituximab complies with the legal criterion 'established medical science and medical practice' for the treatment of adult patients with CLL who have received at least one previous treatment.

This assessment of venetoclax focuses specifically on patients who have received at least one previous treatment (i.e. relapsed or refractory (R/R) CLL). Furthermore, venetoclax was compared with the standard second-line treatment, whereby the choice of treatment depends on whether or not a 17p deletion or a *TP53* mutation is present, and whether the patient has an early or a late relapse:

- In a direct comparative study in the second line, venetoclax (plus rituximab) was more effective on patients without a 17p deletion or *TP53* mutation and with a late relapse than the most frequently used standard treatment with bendamustine (plus rituximab), with an improvement in the 3-year (progression-free) survival.

- Convincing effects were seen both for treatment with venetoclax (plus rituximab) and with the current standard treatment, ibrutinib, on patients

[1] Package Management in Practice 3 (2013). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[2] Assessment of Established Medical Science and Medical Practice: updated version (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

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

with a 17p deletion or *TP53* mutation *or* patients without a 17p deletion or *TP53* mutation but with an early relapse. In view of the limitations of the indirect comparison that had to be conducted, it can be concluded that both treatment strategies are valuable, though without any pronounced preference.

The available information on safety does not reveal any clear differences between treatment with venetoclax (plus rituximab) and the above-mentioned standard treatments.

The use of venetoclax (plus rituximab) in second-line treatment will result in estimated additional costs of €21 to €51 million in the 3rd year after its introduction, depending on the total treatment time (1 or 2 years).

The marketing authorisation holder claims that treatment with venetoclax is cost-effective, with an ICER of circa €50,000 per QALY, on patients without a 17p deletion or a *TP53* mutation and with a late relapse; the group of patients for whom venetoclax has an additional value in comparison with the standard treatment. Due to uncertainties regarding the long-term effectiveness data on survival and the lengthy period of treatment with venetoclax (plus rituximab), the *Zorginstituut* expects its cost-effectiveness to be closer to €65,000 per QALY. The *Zorginstituut* assumes, based on the input of the medical professionals, that the treatment effect of venetoclax (plus rituximab) will be reduced by 5% per year and that treatment will last no longer than 2 years. If, in practice, treatment does continue until disease progression and/or the post-treatment reduction in treatment effect is higher than the 5% that clinicians currently assume, then the cost-effectiveness will be less favourable.

Based on the following considerations, the *Zorginstituut* advises the Minister to start price negotiations.

- Uncertainty exists about the added value of venetoclax (plus rituximab) in comparison with standard ibrutinib treatment for patients with 17p deletion or *TP53* mutation *or* patients without the said deletion or mutation and with an early relapse.

- Due to uncertainty about long-term survival, the *Zorginstituut* concludes that the burden of disease is between 0.67 and 0.76. As the break-even point for the cost-effectiveness reference value is at a burden of disease of 0.7, uncertainty exists about the 80,000 euro/QALY reference value used, which applies to the highest burden of disease. If one assumes a lower burden of disease than 0.7, then treatment with venetoclax is not cost-effective.

- It is as yet uncertain whether the maximum treatment duration, as cited in the registration text and confirmed by medical professionals, will not be exceeded in practice.

- The budget impact is high and could increase even further due to uncertainties about the duration of treatment. This could lead to displacement.

- Venetoclax is already being reimbursed from the basic insurance for the same disorder but in a different line of treatment. Volume is increasing as a result and development costs are being recouped more quickly.

Appropriate use
The HOVON states that patients will be treated with venetoclax for 2 years at most, and not always until disease progression occurs. Furthermore, the HOVON states that, assuming comparative effectiveness and costs, in practice, treatment with venetoclax or ibrutinib can be chosen for patients with a 17p deletion or *TP53* mutation *or* patients without the said deletion or mutation and with an early relapse.

Evaluation
If venetoclax is accepted into the insured package based on the outcome of price negotiations, the *Zorginstituut* will actively monitor its use. The *Zorginstituut* plans to inform the Ministry in 2022 about the results of these measurements.

The *Zorginstituut* will review, among other things:

- The extent to which the number of patients originally estimated agrees with the number of patients actually treated;
- Cost developments relative to the original estimation, part of which is monitoring the actual price of venetoclax;
- Care consumption with a view to assessing points of departure for appropriate use.

If this monitoring indicates strong discrepancies from the current estimates, this may be a reason for the *Zorginstituut* to reassess the position of venetoclax.

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The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.