



> Return address PO Box 320, 1110 AH Diemen

To the Minister of Health, Welfare and Sport
P.O. Box 20350
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2025015938

Date 14 July 2025
Re: Package advice lock procedure medicinal product venetoclax
(Venclyxto®) for chronic lymphocytic leukaemia (CLL)

**National Health Care
Institute**

Research, Development and
Medicinal Products
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Dear Ms Jansen,

The National Health Care Institute advises you on the assessment of venetoclax (Venclyxto®) for previously untreated groups of patients with three subtypes of chronic lymphocytic leukaemia (CLL). This advice was prompted by the placement of venetoclax in the package lock for expensive medicinal products for previously untreated CLL.

The National Health Care Institute advises you to include venetoclax in combination with obinutuzumab in the basic healthcare package for the indication of fit, previously untreated patients with CLL and mutated IGHV status, without 17p depletion (del(17p)) and/ or TP53 mutation. The condition is that the net price is equal to the net price of the standard treatment.

The National Health Care Institute advises you to not include venetoclax in combination with obinutuzumab in the basic healthcare package for the indications:

- fit, previously untreated patients with CLL and an unmutated IGHV status, without del(17p) and/or TP53 mutation, and
- previously untreated patients with a del(17p) and/or TP53 mutation.

Clinical picture

Chronic lymphocytic leukaemia (CLL) is a cancer of one of the white blood cells, the B cells. These cells continue to multiply, do not die and do not function properly. Eventually, they accumulate in the blood, lymph nodes, bone marrow, spleen or liver and displace the healthy cells.

CLL can be caused by different changes in the genetic material of the cell, leading to different variants of CLL. In 2023, 937 people in the Netherlands were diagnosed with CLL. It is the most common form of leukaemia and is especially prevalent in patients older than 60 years. On average, three-quarters of patients are still alive after 10 years. CLL develops slowly. It is only treated when symptoms occur, such as infections, fatigue due to anaemia, spontaneous bleeding or swelling. Venetoclax inhibits the survival of abnormal B cells. Depending on patient fitness and disease variant, previously untreated patients are treated with chemo-immunotherapy, acalabrutinib, ibrutinib or zanabrutinib, and/or venetoclax. We therefore distinguish between different patient groups.

Registered indication

Venetoclax (Venclyxto®) in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Venetoclax has been registered and is reimbursed for additional CLL and AML (acute myeloid leukaemia) related diseases. This assessment pertains solely to the above indication.

Claim by the marketing authorisation holder

Venetoclax (Venclyxto®) in combination with obinutuzumab for:

- 1) fit, previously untreated CLL patients with IGHV mutation, without del(17p) and/or TP53 mutation, has an equal value to chemo-immunotherapy (CIT).
- 2) fit, previously untreated CLL patients without IGHV mutation, without del(17p) and/or TP53 mutation has added value over CIT.
- 3) previously untreated CLL patients with del(17p) and/or TP53 mutation has an equal value to ibrutinib or acalabrutinib.

Package advice

The National Health Care Institute recommends that venetoclax (Venclyxto®) in combination with obinutuzumab for the treatment of fit, previously untreated patients with CLL with an IGHV mutation, without del(17p) and/or TP53 mutation (1) be included in the base package, provided that the net price after successful price negotiations does not exceed the net price of chemo-immunotherapy. The National Health Care Institute has determined that venetoclax in combination with obinutuzumab meets the legal criterion of 'established medical science and medical practice' for the indication mentioned. There is an added value compared to standard treatment with chemo-immunotherapy.

The National Health Care Institute recommends that venetoclax (Venclyxto®) in combination with obinutuzumab for the treatment of fit, previously untreated CLL patients without IGHV mutation, without del(17p) and/or TP53 mutation (2) should not be included in the basic healthcare package. The National Health Care Institute has determined that venetoclax meets the legal criterion of 'established medical science and medical practice' for the indication mentioned. There is an added value compared to standard treatment with chemo-immunotherapy. The negative advice is based on the cost-effectiveness analysis provided by the marketing authorisation holder. It is not of sufficient quality, even after the marketing authorisation holder was given the opportunity to correct the analysis.

The National Health Care Institute recommends that venetoclax (Venclyxto®) in combination with obinutuzumab for the treatment of previously untreated CLL patients with del(17p) and/or TP53 mutation (3) should not be included in the basic healthcare package. The National Health Care Institute has established that venetoclax does not meet the legal criterion of 'established medical science and medical practice' for this indication.

We explain the preparation of this package advice below.

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General

At your request, the National Health Care Institute assesses whether care should be part of the standard health insurance package from the perspective of the basic healthcare package paid from joint premiums.

The National Health Care Institute assesses on the basis of the four package criteria¹: effectiveness²cost-effectiveness³, necessity⁴ and feasibility⁵. The Scientific Advisory Board (WAR) advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. Stakeholders are consulted during the process.

Comprehensive weighting of package criteria

Effectiveness

Established medical science and medical practice

1) Fit, previously untreated CLL patients with IGHV status without del(17p) and/or TP53 mutation: In the randomised, open-label phase III study (RCT) GAIA-CLL13, venetoclax obinutuzumab was compared with chemo-immunotherapy in patients without del(17p) and/or TP53 mutation. The assessment was made for the subgroup with an IGHV mutation. The National Health Care Institute concludes that there are no clinically relevant differences in survival data, adverse effects and risk of discontinuation between the two groups. Survival has been assessed by the surrogate outcome progression-free survival. The National Health Care Institute, advised by the WAR, concluded that venetoclax-obinutuzumab in the indication mentioned meets the established medical science and medical practice, and has an equivalent value to chemo-immunotherapy.

2) Fit, previously untreated CLL patients without IGHV status without del(17p) and/or TP53 mutation: For the assessment of this group, a pre-specified subgroup analysis of patients without an IGHV mutation from the same study as above was assessed. Quality of life data was not available. Based on a potentially clinically relevant improvement on survival and no clinically relevant differences on adverse effects and risk of discontinuation, the National Health Care Institute, advised by the WAR, concludes that venetoclax-obinutuzumab complies with the established medical science and medical practice. Survival is assessed as a means of surrogate outcome measure progression-free survival. Venetoclax-obinutuzumab has added value compared to chemo-immunotherapy.

3) Previously untreated CLL Patients with a del(17) and/or TP53 mutation: This is a reassessment. According to the professional group, venetoclax-obinutuzumab is the second choice for this subgroup of CLL patients, after ibrutinib and acalabrutinib. In 2020, the National Health Care Institute concluded that

¹ Real-world package management 4 (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

² Assessment of the established medical science and medical practice (2023). National Health Care Institute. Via www.zorginstituutnederland.nl.

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

⁴ Necessity is related to both the medical need due to the severity of a disease for the patient (burden of disease) and the need to insure something. See the report on real-world package management 4 (2023).

⁵ The package criterion of feasibility deals with whether it is feasible or sustainable to include a specific form of care in the basic healthcare package. It is therefore mainly a test of a number of implementation aspects, such as the healthcare organisation, the support base, ethical and legal aspects, budget impact, etc. See the report on real-world package management 4 (2023).

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venetoclax-obinutuzumab did not meet the established medical science and medical practice due to insufficient evidence. At the time, the combination was compared with ibrutinib, for which no new relevant publications are yet available. In the meantime, the National Health Care Institute has determined that acalabrutinib and ibrutinib are of equal value. Since RCT data are now available for venetoclax-obinutuzumab and acalabrutinib with the same comparator control group, this reassessment was compared to acalabrutinib. This is based on an indirect comparison of two randomised, open-label phase III studies in patients comparing venetoclax-obinutuzumab and acalabrutinib to chlorambucil-obinutuzumab; the CLL14 and ELEVATE-TN studies, respectively. Venetoclax-obinutuzumab appears to have a lesser effect on survival as measured by progression-free survival. The adverse effects and the risk of discontinuation cannot be ruled on. The National Health Care Institute, advised by the WAR, concluded that venetoclax-obinutuzumab for the indication mentioned does not meet the established medical science and medical practice. This is in line with the WAR advice. The CLL17 study directly compares venetoclax-obinutuzumab with, among others, ibrutinib monotherapy. This study can assess the actual value of venetoclax-obinutuzumab compared to ibrutinib. This study has since been started and will run until September 2027.

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Cost-effectiveness

Only the fit, previously untreated CLL patient group without IGHV mutation and without del(17p) and/or TP53 mutation (2) has demonstrated an added value. Therefore, the National Health Care Institute has only assessed the cost-effectiveness for this group.

However, the cost-effectiveness analysis provided by the marketing authorisation holder is of insufficient quality. As a result, the National Health Care Institute cannot provide a methodologically reliable estimate of cost-effectiveness. Specifically, the marketing authorisation holder has not performed the additional analyses requested by the National Health Care Institute. As a result, the impact of certain relevant factors on cost-effectiveness could not be determined. Consequently, the pharmaco-economic analysis is insufficiently transparent and shows a lack of quality and representativeness. Therefore, a scientifically valid and reliable statement on the cost-effectiveness of venetoclax combined with obinutuzumab for this patient group is not possible. As such, the National Health Care Institute cannot reliably advise you regarding any price negotiations. The National Health Care Institute realises that the outcome of this assessment is disappointing for patients with this indication and their treating physicians. The National Health Care Institute therefore expressly invites the marketing authorisation holder to make the necessary adjustments⁶ in the pharmacoeconomic analysis.

Budget impact analysis

A total of 342 patients are estimated to be eligible for treatment for the claimed indications. These are 154 patients in the first two groups, and 34 in the third subgroup. The BIA has only been performed for the two groups that comply with the established medical science and medical practice (1 and 2). The National Health Care Institute estimates that in year 3 after (hypothetical) reimbursement, 14 patients from group 1 and 46 patients from group 2 would be treated with

⁶ In case of resubmission, additional unsolicited adjustments to the PE model will not be accepted.

venetoclax-obinutuzumab. Seeing that no positive package opinion can be reached for group 2 due to the insufficient pharmacoeconomic model, only the budget impact of group 1 is highlighted here. The group 2 BIA is set out in the Annex.

The total cost per patient per year for fit previously untreated CLL patients with IGHV mutation and without del(17p) and/or TP53 mutation (1) comes to €72,455. Fludarabine-cyclophosphamide rituximab (FCR) and bendamustine-rituximab (BR 90) are substituted, with a cost per patient of €14,911 and €15,131 respectively. This results in macro costs of € 516,053 in the third year. When substitution of FCR and BR90 is also taken into account, the budget impact in year 3 is €396,107. However, there is uncertainty about the number of patients receiving first-line treatment, market penetration, and the distribution between FCR and BR90. In addition, the calculations are based on list prices, while the prices of the comparative treatment may be lower. Given the equal value for this group, the net price after successful price negotiations should not exceed the net price of chemo-immunotherapy (FRC or BR 90).

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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