Zorginstituut Nederland

g> Return address PO Box 320, 1110 AH Diemen

Minister of Medical Care and Sports
Care of: GMT Management
PO Box 20350
2500 EJ THE HAGUE

2020033310

National Health Care Institute
Business services
Automation

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

Contact
Ms J.E. de Boer
T +31 (0)6 215 833 54

Our reference
2020033310

Date 14 September 2020
Subject Package advice ibrutinib in case of Waldenstrom's disease

Dear minister van Ark,

At your request, Zorginstituut Nederland has assessed the medicinal product ibrutinib (Imbruvica®) in combination with rituximab for the indication: Waldenstrom macroglobulinemia (WM).

Based on this assessment, I recommend that you do not include ibrutinib in combination with rituximab in the basic package for this indication. In this letter, I will explain this advice.

History
Your predecessor placed ibrutinib in combination with rituximab for the above indication in the package lock for expensive medicines, at the same time as the application of ibrutinib in combination with obinutuzumab as a primary care treatment for patients with chronic lymphatic leukaemia (CLL). We recently (3 July) sent your predecessor a package advice on this latter application (reference 2020026276).

Assessment
Because ibrutinib in combination with rituximab is not included in the current guideline for the treatment of WM, we have consulted the Netherlands Association for Haematology as the first step of our assessment of the position of ibrutinib in the treatment of this disease.

The position of ibrutinib in the treatment
Ibrutinib is only used sporadically in primary care treatment: when patients are not fit enough to undergo treatment with chemoimmunotherapy. Ibrutinib is currently mainly used for recurrent treatment (usually from the 2nd recurrence and after, which is more common in chemoimmunotherapy-refractory patients or in patients not fit enough for chemoimmunotherapy).

The WM guideline is currently under review. The Netherlands Association for Haematology states that ibrutinib in combination with rituximab does not have a standard position within the new guideline. The reason for this is that the added

value of the addition of rituximab to ibrutinib has not been investigated.

In the INNOVATE study, the addition of ibrutinib to rituximab was investigated in relation to rituximab monotherapy. In Dutch practice, however, monotherapy with rituximab has little or no place in the treatment of WM. This study therefore does not provide sufficient justification for the added value of the addition of rituximab to the treatment with ibrutinib.

The practitioners also indicate that there might be a very limited role for the addition of rituximab to ibrutinib to deepen the response in patients for whom the ibrutinib dose should be reduced due to toxicity or in patients on ibrutinib monotherapy with an insufficiently deep response and for whom there are no good alternatives. The Netherlands Association for Haematology states that this will only be advised in exceptional cases (several patients per year), because the side effects of the combination therapy, compared to ibrutinib monotherapy (e.g. sensitivity to infection), have not been properly investigated.

Advice
On the basis of the available INNOVATE study and the statements above, the conclusion is that the use of this combination does not belong to established medical science and medical practice. This also applies to the very limited room that the Netherlands Association for Haematology sees for the addition of rituximab to ibrutinib, because there is no justification for this application from clinical research. The Zorginstituut therefore advises you not to include ibrutinib in combination with rituximab in the basic package.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

National Health Care Institute
Business services
Automation

Date
14 September 2020

Our reference
2020033310