Zorginstituut Nederland

> 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

2020026917

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
2020026917

Date 03 July 2020
Subject Package advice for ibrutinib (Imbruvica®)

Dear Mr van Rijn,

Zorginstituut Nederland has completed the assessment of ibrutinib (Imbruvica®) for the indication as monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphatic leukaemia (CLL). Based on this assessment, I recommend to include ibrutinib in the basic health care package, after successful price negotiations on the basis of a realistic (in principle) public price proposal from the manufacturer. In this letter, I will explain this advice.

You have placed ibrutinib in the 'lock procedure' for expensive medicines for the indication mentioned above. The Zorginstituut assessed ibrutinib on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. From the point of view of the basic package paid from joint premiums, the Zorginstituut makes the assessment of whether new care should be part of the insured package. We look at the degree of certainty that this will be achieved, both in the scientific sense, as well as in the public support, and we look at aspects of efficiency and transparency. The Zorginstituut is advised by two independent committees: the Scientific Advisory Council (WAR) for the scientific and practical assessment of the data and the determination of the cost-effectiveness, and the Package Advisory Committee (ACP) for the social assessment. We also consulted interested parties during the assessment process.

History

Ibrutinib has an orphan drug status. It has already been assessed (mid 2017) by the Zorginstituut, at the request of the Minister (as part of the 'lock procedure'), for the indication of monotherapy in patients with previously untreated CLL, without a del17p or TP53 mutation. For patients *with* these mutations, ibrutinib was already included in the package as primary care treatment at that time.

[1] Real-world package management 3 (2013). National Health Care Institute, 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

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The advice of the Zorginstituut to you was to include ibrutinib only in the insured package for the subgroup of patients with CLL who are included in the established medical science and medical practice: the subgroup of older, unfit patients without del17p or TP53 mutation for whom the use of anti-CD-20 is contraindicated or has more disadvantages than benefits to the patient.

To ensure the accessibility and affordability of the package, we also advised to ask the Zorginstituut for a reassessment if new data were to become available. The primary reason for this was the potentially large budget impact. The second reason was that if new data were to become available for use in a wider group of CLL patients without del17p or TP53 mutation for which a therapeutic inferior value was then established, or in the case of an expansion of the indication for ibrutinib.

You have adopted this advice and since new data is now available, you have asked us to reassess ibrutinib for the primary care treatment application for the subgroup for which there is currently no reimbursement.

Package advice (conclusion)
Ibrutinib now meets the established medical science and medical practice for the entire group of adult patients with previously untreated CLL without del17p or TP53 mutation:

- fit patients ≤ 65-70 years and an unmutated IGHV
- fit patients > 65-70 years
- unfit patients.

Treatment with ibrutinib provides a clinically relevant improvement in the progression-free survival of at least 6 months compared to the standard treatment applied to the patients that were mentioned. It is still unclear whether ibrutinib will also lead to an improved survival compared to standard treatment. The undesirable effects of ibrutinib are acceptable. Compared to current therapies, ibrutinib has the advantage that it can be administered orally.

The costs for a full year's treatment with ibrutinib in the first line of treatment are €69,839 per patient. The treatment with ibrutinib lasts on average 3 years. Based on approximately 445 patients per year who will be treated with ibrutinib, the total cost of treatment is estimated at €22.1 million per year when taking into consideration the substitution of the current treatments.

The Zorginstituut presents a large range of the cost-effectiveness of ibrutinib due to uncertainty about the effect on overall survival: for the entire patient group, it is roughly between €60,000 and €200,000 per QALY. For a condition with an average burden of disease (for previously untreated CLL patients, it is between 0.45 and 0.56), which applies to these patients, a reference value of €50,000 per QALY applies.

Ibrutinib has already been registered for several indications and is included in the basic insured package here in the Netherlands and in other countries. In any case, the investments made by the manufacturer have already been partially recovered. This justifies a lower price below the reference value. I would stress that there is still uncertainty about the influence of ibrutinib on the overall survival and quality of life of patients with CLL. Furthermore, the registered indications of ibrutinib will be extended in the coming years.

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This means that the price reduction from a social perspective must be much more substantial than what is now mentioned in the pharmaco-economic report (25% to a maximum of 75%).

The appendix contains the advisory report of the ACP to the Zorginstituut's Executive Board. You will notice that the advice of the ACP is different from the advice I am giving you. I would like to explain this: in its public discussion, the ACP takes a clear position in the debate on the high prices of medicinal products. The ACP's advisory report is a logical result of this debate and is consistent with the criteria and arguments put forward by the members of the ACP. The Executive Board follows the analysis and considerations of the ACP, but wants to change the 'no, unless' to a 'yes, provided that', to slightly expand the negotiation room for discussions with the supplier on pricing.

In view of all this, I recommend that you proceed to price negotiations and inclusion in the package. I would like to recommend that you invite the manufacturer to come up with a publicly available realistic price proposal. Like the ACP, I believe it is important to increase transparency about the pricing of medicines. I also think it is important that the manufacturer also takes on its social responsibility in a visible and verifiable way.

Yours sincerely,

Peter Siebers
Interim Chair of the Executive Board