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2020051347

Date 10 December 2020
Subject Package advice polatuzumab vedotin (Polivy®)

Our reference
2020051347

Dear Mrs van Ark,

The National Health Care Institute is hereby advising you about polatuzumab vedotin (Polivy®), in combination with bendamustine and rituximab (Pola-BR) in the treatment of adults with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL, a form of lymphoma) who are not eligible for hematopoietic stem cell transplantation (SCT). The reason for this advice was the placing of the appointed medicinal product in the so-called 'package lock' for expensive medications.

The National Health Care Institute assessed Pola-BR 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, while Pola-BR is an effective medicinal product for these patients, there are arguments to advise you to engage in price negotiations.

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 insured package paid from joint premiums. The National Health Care Institute is advised by two independent committees: the Scientific Advisory Board (WAR) for advice on established medical science and medical practice and on cost-effectiveness, and the Insured Package Advisory Committee (ACP) for the appraisal. The National Health Care Institute has also consulted relevant stakeholders during the assessment procedures.

[1] Real-world package management 3 (2013). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

[2] Established medical science and medical practice assessment: updated version (2015). National Health Care Institute,
Diemen. Via www.zorginstituutnederland.nl

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

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Integral weighting of package criteria

Established medical science and medical practice

DLBCL is a type of lymphoma. It belongs to the group of non-Hodgkin lymphomas. The treatment of DLBCL involves many stages of treatment. The standard first-line treatment for DLBCL consists of immuno-chemotherapy with an R-CHOP regimen. Second- and third-line treatment depends (partially) on the patient's level of fitness. It can involve chemotherapy, radiation, stem cell transplantation or CAR-T cell-therapy (or a combination of the above). There are no established treatment options for patients with r/r DLBCL who are not eligible for SCT (stem cell transplantation). In Dutch clinical practice, palliative treatment involving a combination of rituximab, prednisone, etoposide, lomustine and chlorambucil (R-PECC) or, less often, bendamustine and rituximab (BR) is usually used in these patients. Neither of these treatments is registered for these applications.

According to clinical experts, Pola-BR will be used in Dutch clinical practice as:

- second-line palliative treatment for patients who are not fit enough for autologous SCT
- third-line palliative treatment for patients who were not fit enough for autologous SCT during second-line treatment or who underwent second-line autologous SCT but are not fit enough to start an allogeneic SCT procedure and who are also not fit enough for CAR-T cell-therapy or cannot wait for the preparation of patient-specific CAR-T cells.

This letter is confined to the main conclusions. Should you require more detailed information then I would refer you to the Pharmacotherapeutic report. The substantiation for the Pola-BR claim is a phase 2 study, which had various limitations. For example, it did not contain data concerning quality of life. Furthermore, while the comparative treatment can be used as a proxy, this is not often used in the Dutch patient population. Accordingly, based on this phase 2 study, it is difficult to make a definitive statement concerning the relative difference in overall survival between Pola-BR and BR in adults with r/r DLBCL who are not eligible for SCT. The median overall survival was 12.4 months (95% CI 9.0; not reached) in the Pola-BR arm compared to 4.7 months (95% CI 3.7; 8.3) in the BR arm, which corresponds to a median absolute gain of 7.7 months when polatuzumab is added to BR (HR = 0.42 (95% CI 0.24; 0.75)). Here, we have taken account of the fact that the clinical professionals consider a difference of three months to be clinically relevant. Based on the terminology of the Grade methodology, we conclude that this major effect reported by the study suggests that Pola-BR may lead to a clinically relevant advantage over BR in this patient population.

Budget impact

Based on the market authorisation holder's claim, data from the Horizon scan supplemented with input from clinical professionals, the National Health Care Institute estimates that a minimum of 163 and a maximum of 288 patients for the appointed indication will be treated with Pola-BR in the third year after inclusion in the Dutch basic healthcare insurance package. The registration study involved an average treatment duration of 4.4 cycles. The annual cost of Pola-BR is €55,849 per patient (€45,399 + (4.4 * €2,375)). Including substitution, the additional costs charged to the pharmaceutical budget amount to a minimum of €7.6 million and a maximum of €13.5 million in the third year after inclusion in the Dutch basic healthcare insurance package.

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Cost-effectiveness
In this letter, I will confine myself to the main conclusions. Should you require more detailed information, then I would refer you to the Pharmaco-economic report. Despite a number of uncertainties in the pharmaco-economic model, the National Health Care Institute concludes that the cost-effectiveness analysis is of sufficient methodological quality. The National Health Care Institute considers the assumptions regarding post-treatment quality of life to be too optimistic. It has requested an additional scenario analysis using calculations based on a poorer quality of life. According to that analysis, this results in an increase in the costs per QALY, probably to approximately €60,000 per QALY.
The deterministic incremental cost-effectiveness ratio (ICER) in the base case analysis is estimated at €48,477 per QALY, compared to the standard treatment. The National Health Care Institute concludes that, at a reference value of €80,000 per QALY, Pola-BR is cost-effective compared to the standard treatment.

Package advice
In view of the uncertainties discussed above, the National Health Care Institute deems it inappropriate to issue positive advise without any conditions. Accordingly, it advises you to engage in price negotiations. There are a number of arguments in favour of negotiating a price below the reference value. The treatment extends life and is not curative, also there is still some uncertainty about the quality of life during the months of life gained. In addition, due to the above-mentioned uncertainty concerning effectiveness and, by extension, cost-effectiveness, it is deemed appropriate to negotiate a price below the reference value.
In addition, there is a lack of long-term data and, in due course, a new ruling should be issued concerning the continuation of the reimbursement for this medicinal product. A pay-for-proof price agreement, stating that a higher price will be paid when more evidence becomes available, may also be an option. If that proves not to be the case, then the negotiation will have to result in an even more competitive price. Finally, one argument that could be used in price negotiations is that studies are underway into the use of this medicinal product in first-line treatment, which may lead to an increase in patient volume.

All things considered, the National Health Care Institute recommends that Pola-BR (Polivy®) be reimbursed once price negotiations have been completed. There are demonstrable grounds for negotiating a price below the reference value of €80,000 per QALY. In view of the uncertainties involved, the medical-ethical aspect associated with quality of life, and the anticipated extension of indication.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board