Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

National Health Care Institute

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
F. van den Berg
T +31643470635

2024035367

Date 27 January 2025
Re: Package advice multiple myeloma 2025

Our reference
2024035367

Dear Ms Agema,

The National Health Care Institute informs you in the attached report about the results of the pilot that started as a follow-up to the package advice we have issued on a number of combinations of lock procedure medicinal products for the treatment of multiple myeloma (MM).

Background
MM, also known as Kahler's disease, is a bone marrow cancer. The disease cannot be cured, but many new medicinal products have become available in recent years, leading to longer survival of patients live. However, the cost of the treatments is very high.

In 2021, the National Health Care Institute sent two package advice reports on combinations of lock procedure medicinal products for MM to your predecessor (dated 11 February and 25 May 2021).[1] [2] These concerned various indications for medicinal product combinations with daratumumab, pomalidomide, carfilzomib and isatuximab. The National Health Care Institute concluded in the above-mentioned advisory reports that the effectiveness of these medicinal products has been adequately demonstrated. The National Health Care Institute does not consider the assessment of some individual treatment combinations in a particular treatment line to be the right instrument to address questions regarding insured health care coverage, its affordability and use of resources for MM. The reason for this is the application of these combinations in a dynamic treatment landscape. Another factor is that for patients with MM, not the best (combination) treatment per treatment line is the most relevant, but the best outcome overall after several treatment lines,. For this reason, the National Health Care Institute announced that an alternative, indication-wide approach to the advice on the use of the medicinal products for MM would be developed in a pilot.

In addition, the National Health Care Institute advised your predecessor to

[1] Package advice 6 treatment combinations of medicinal products for multiple myeloma. To be consulted via: Pakketadvies 6 behandelcombinaties van geneesmiddelen bij multipel myeloom | Advies | Zorginstituut Nederland.

[2] Package advice lock procedure medicinal product isatuximab (Sarclisa). To be consulted via: Pakketadvies sluisgeneesmiddel isatuximab (Sarclisa®) | Advies | Zorginstituut Nederland.

conditionally include the assessed MM medicinal products during the pilot period and after rigorous price negotiations in the basic health care package until a final approach and advice was realised by the National Health Care Institute. This because of the interest of patients with MM that the combination therapies mentioned became available.

Pilot period
During the pilot period, the National Health Care Institute studied the complete indication for MM. It involved a task group (treating physicians, patients, health insurers) and a sounding board group (marketing authorisation holders). The National Health Care Institute commissioned a disease model for MM patients who are not eligible for stem cell transplantation and prepared a budget impact analysis for the MM medicinal products in the lock procedure. There was no reason to re-evaluate the established medical science and medical practice (SWP) for MM lock procedure medicinal product indications.

Development and validation of the disease model
Because the traditional way of assessing individual medicinal products does not reflect the effectiveness and cost-effectiveness of successive MM treatments, the National Health Care Institute has commissioned the Erasmus School of Health Policy & Management (ESHPM) to (further) develop a disease model for the group of MM patients not eligible for stem cell transplantation. This is the group of patients for which most new, often expensive, medicinal product combinations have become available in recent years.

The MM disease model is a pharmaco-economic model that provides insight into the expected health benefits of 59 different treatment sequences (QALYs), the expected treatment costs, and thus the cost-benefit ratio. The disease model specifically looked at the (cost) effectiveness of successive MM medicinal product treatments for patients not eligible for stem cell transplantation (SCT). Data from scientific studies and from Dutch practice (IKNL data) was used for this purpose. Treating physicians have identified the 59 treatment sequences studied as relevant for the treatment of patients.

The ESHPM researchers have assessed the costs of medicinal products as realistically as possible by using reimbursement data (Vektis) and a scenario analysis with an estimate of the average price reduction of the lock procedure medicinal products negotiated by the Ministry of VWS (BFAG).[3]

The results of the assessment based on the disease model have been presented by the National Health Care Institute and discussed in the Scientific Advisory Board (WAR). In addition, a technical validation of the disease model was carried out by an independent qualified party. Stakeholders were also consulted. Finally, a societal deliberation took place at a public meeting of the Insured Package Advisory Committee (ACP).

Main findings of the disease model MM non-SCT
Through the development of the disease model by ESHPM we have gained insight into the (cost) effectiveness of different treatment sequences for MM. The disease model shows that MM patients who are not eligible for stem cell transplantation

[3] BFAG: Buro Financiële Arrangementen Geneesmiddelen (office for financial arrangements of medicinal products).

live longer thanks to the use of new medicinal products. But it also shows that in the vast majority of treatment sequences, expenditure on MM resources is not in proportion to the health benefits achieved and significantly exceed acceptability thresholds in the Netherlands. The attached report includes the discount rates needed to achieve cost-effective care.[4]

The MM disease model shows that treatment sequences beginning with daratumumab in the first treatment line provide the most healthy life years for the patient. This is in line with the preference of the treating physicians for daratumumab in combination with lenalidomide and dexamethasone (DaraRD) for first line treatments. However, sequences with DaraRD in first line treatments are even more expensive than other treatment sequences and not cost-effective at the current asking price.

Budget impact analysis (BIA)
The products we advised on in 2021 (daratumumab, carfilzomib, isatuximab and pomalidomide) are also used in other combinations or as monotherapy for patients with MM. To estimate the total cost of all existing indications of these products, we have made a BIA for the next three years (2025 to 2027).

The BIA shows that the total expenditure for daratumumab is expected to be €338.2 million in 2027. For patients not eligible for SCT, the cost of daratumumab is expected to increase over the next three years due to an increase in first line treatment use, while patients in secondary (or later) treatment lines are still being treated (with daratumumab) at the same time. After three years a decrease is expected as patients receiving daratumumab in first line treatments will not be treated with it again (in later treatment lines).

For the group of patients eligible for SCT, no significant increase in daratumumab expenditure is expected. Since daratumumab is already the current standard for induction, consolidation and secondary line treatment, an increase in expenditure is expected only due to the annual increase in the number of diagnoses.

For carfilzomib and isatuximab we do not expect major changes in the total costs over the next three years (2025 to 2027) for the *existing* indications. The expected costs for carfilzomib and isatuximab are expected to be €28.1 million and €10.0 million respectively in 2027.

Appropriate use
The disease model shows that there are significant differences in the (cost) effectiveness of different treatment sequences. These outcomes can be taken into account by the treating physicians in determining the most appropriate care, in consultation with the patients.

Unfortunately, in the Netherlands, there is still no effective national register that provides sufficient reliable and practical information on the effectiveness and cost-effectiveness of medicinal products. However, there are subsets (e.g. at IKNL) or dashboards based on hospital data. The National Health Care Institute continues to plead for good data records that allow for the evaluation of practical use.

[4] 'Indication-wide assessment of multiple myeloma for patients not eligible for stem cell transplantation'.

In addition, the professional association can develop initiatives to improve the care for patients with MM and make it more (cost)effective. In this context, the FABULOUS study initiated by the professional association is a good example. This (cost)effectiveness study will determine if a lower treatment burden can be achieved for the patient with a identical effectiveness.

Key points of the advice

- The disease model is a subpopulation of MM patients, namely those who are not eligible for a stem cell transplant.
- One of the combination therapies included in the package recommendation of 2021 (i.e. daratumumab, bortezomib, thalidomide, dexamethasone (DaraVTD)) is intended for newly diagnosed patients with MM who do receive an initial stem cell transplant. This group falls outside the scope of the MM disease model and has not been investigated as part of it. This combination is now no longer prescribed. It has been replaced by the off-label combination therapy daratumumab, bortezomib, lenalidomide, dexamethasone (DaraVRD)). This off-label indication has not been assessed by the National Health Care Institute.
- Carfilzomib and isatuximab are also prescribed to patients who have received a stem cell transplant. Two-thirds of carfilzomib use involves patients who do undergo a stem cell transplant.
- For the medicinal products lenalidomide and pomalidomide, the lock (financial) agreements have since been discontinued (on 1 March 2022 and 11 October 2024 respectively). The expiry of the patent and the admittance of generic suppliers to the market have shown that stakeholders can tackle the financial risk of high macro-cost impact themselves. Since they are no longer lock procedure medicinal products, the National Health Care Institute will not advise on these medicines within the MM pilot.

Advice

On the basis of the above, the National Health Care Institute recommends that new price agreements be made to keep healthcare in the Netherlands affordable and to guarantee access to new treatments for patients, now and in the future. The disease model for patients who are not eligible for SCT shows that MM patients live longer thanks to the use of new medicinal products, but that prices determined by pharmaceutical companies are not in proportion to the added value. The assessment report 'Indication-wide assessment of multiple myeloma for patients not eligible for stem cell transplantation' includes information to be used to achieve cost-effective care for this group of MM patients.

Based on this report, the National Health Care Institute advises the Minister to negotiate with the manufacturers of daratumumab, carfilzomib and isatuximab to keep the treatment sequences that are most effective for patients available at a socially acceptable price. It is important to take note of the fact that the greatest health benefits in patients not eligible for SCT are achieved with the use of daratumumab combinations in first line treatments. The treating physicians have a preference for daraRD in primary healthcare. The results of the disease model, as well as the prepared BIA, also provide points of reference for conducting the new price negotiations on the lock procedure medicinal products for multiple myeloma.

We advise you, during upcoming price negotiations, not to take into account the

expected results from (ongoing) (cost)effectiveness studies, since the results on effectiveness and costs savings are uncertain.

We advise the medical association, in the context of appropriate care, to be aware of differences in effectiveness, but also of the cost-effectiveness, of different treatment sequences that have been studied within the disease model. The National Health Care Institute expresses its appreciation for the initiatives, such as the FABULOUS study, initiated by the treating physicians to improve MM care and its (cost)effectiveness for patients . Funding of and support for such research is necessary. To achieve sufficient impact of this study, it is important that this study has a high inclusion rate. But also that the results are swiftly implemented nationally afterwards.

This advisory report concludes the pilot period, and the regular assessment procedure for MM medicinal products will be resumed. To better implement cyclical insured care package management, the National Health Care Institute has a multi-year research program for the application of disease models in assessing treatments. The development of the MM advice and the experience with the MM-disease model will be taken into account in policy development.

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board