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Date 11 February 2021
Subject Package advice multiple myeloma

National Health Care Institute
Business services
Automation

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Our reference
2020033721

Dear Mrs van Ark,

Your predecessor placed several combination therapies that are used to treat multiple myeloma in the lock procedure for expensive medicinal products, due to the expected disproportionately high cost of use. In this context, you have asked the National Health Care Institute to advise on whether or not these medicinal products (in combination therapy) should be included in the health care package. In this letter, I would like to inform you of this advice.

Summary
The National Health Care Institute is of the opinion that the effectiveness of the medicinal products placed in the lock procedure, which are used in different treatment combinations, is sufficiently demonstrated. However, given the special nature of the multiple myeloma indication, the National Health Care Institute has concluded that isolated individual assessments of the mentioned medicinal products (in combination therapy) do not have sufficient added value from the perspective of the health insurance package. In this indication, the coherence of the different treatment lines, the application of the combinations and the affordability of the whole treatment are important. For this reason, the National Health Care Institute intends to launch a pilot programme to implement and develop an alternative, indication-wide approach. To this end, the National Health Care Institute will set up a task force that represents the stakeholders. In this context, and given the importance of treating patients with multiple myeloma, we advise you to allow the medicinal products placed in the lock procedure be temporarily admitted to the basic insurance after keen price negotiations, pending the advice on this indication from the National Health Care Institute.

Background
Multiple myeloma (MM) is a malignant disease of the bone marrow with an unknown cause. The symptoms occur gradually and arise from disturbed blood production, bone problems, increased calcium levels in the blood and kidney problems. It is also accompanied by increased susceptibility to infections. It is estimated that approximately 1100 patients, mostly aged 65 years or older, are diagnosed annually in the Netherlands. The median survival rate of patients with MM depends greatly on the possibility of undergoing an autologous stem cell

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transplant, the patient's fitness and access to new medicines; the rate varies globally from 2-9 years.

Six medicinal products (all combination therapies) have been placed in the lock procedure, requesting the advice of the National Health Care Institute.

Patients who are *not* eligible for autologous stem cell transplantation:

- Primary care treatment
  - bortezomib, **lenalidomide** and dexamethasone
  - **daratumumab**, bortezomib, melphalan and prednisone
  - **daratumumab**, lenalidomide and dexamethasone
- Secondary healthcare treatment or later stage treatment
  - **pomalidomide,** lenalidomide
  - **carfilzomib**, daratumumab, dexamethasone

Patients who are eligible for autologous stem cell transplantation:

- **daratumumab**, bortezomib, thalidomide and dexamethasone

The medicinal products from the combination therapies mentioned above are all currently used in other combinations and/or treatment lines for multiple myeloma. These and other combination therapies have been entered in the health care package through open inflow and have therefore not been assessed by the National Health Care Institute.
The proposal we make applies to the abovementioned medicinal product combinations. In the short term, further medicinal products (combinations) are expected to be placed in the lock procedure. Medicinal products (combinations) that are newly placed in the lock procedure, will each time be assessed, after advice from the task force, to determine whether they can immediately be entered into the health care package within the terms of the pilot or whether a separate advice from the National Health Care Institute is warranted.

Package advice for products in lock procedure for multiple myeloma
General
A patient with multiple myeloma generally responds well to the initial treatment being used, but the disease returns in most cases. For this reason, patients are often treated multiple times and with different medicinal products, whether or not in combination. The preference for a particular combination therapy is dictated by the clinical characteristics of the patient and also depends on the response to a previous treatment. The development of new treatment combinations is rapid. This means that the treatment preferences change within a specific treatment line (e.g. change in the preferential initial treatment or in one of the follow-up treatments). But even in the order of successive treatments, preferences can change, partly because the choice for a particular combination in an earlier line affects the outcomes in a later line. All this requires regular adjustment of the treatment guideline by the HOVON Myeloma Working Group (MWG). The decisions in the guideline are based on scientific evidence, i.e. randomized and non-randomized clinical studies or consensus of the expert group. The guideline explicitly clarifies the basis of the decisions. The guiding principle of the guideline is that treatment of patients in a study is essential so that the value of new treatment modalities can be determined.

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Package criteria weighting
The National Health Care Institute considered the following and asked the Insured Package Advisory Committee for advice:
The individual combination treatments placed in the lock procedure are applied in a dynamic treatment landscape, as explained above.
One important factor is that for the patient, the best outcome after several treatment lines, not the best (combination) treatment within each treatment line, is the most relevant. In other words, which order of treatment is the most (cost) effective?

This dynamic also makes it difficult to assess the impact of each combination therapy on the macro budget, because an assessment of the number of patients eligible for a particular treatment combination is quickly made invalid due to new developments. It is also difficult to determine the cost-effectiveness of an individual treatment combination for this reason. After all, the data on which the pharmaco-economic model is based must be in line with Dutch clinical practice. This is difficult to determine when it is subject to rapid change. Because of this dynamic, there is a real chance that our package advice on an individual treatment combination has already been rendered obsolete by the new developments at the time of release. Also, the question remains whether the cost-effectiveness of an individual combination therapy is most relevant, or whether it is more about the most effective use of medicinal products after multiple treatment lines, from the point of view of package management.

Taking all this into consideration, and given the special nature of the multiple myeloma indication outlined above, the National Health Care Institute comes to the following conclusion:

Conclusion
Taking into account the abovementioned dynamics in the treatment landscape, the National Health Care Institute considers the effectiveness of the abovementioned medicinal products used in different treatment combinations sufficiently demonstrated, based on the well-founded (draft) guideline of the Myeloma Working Group and the underlying clinical studies. However, the National Health Care Institute notes that questions remain about in which combination the medicinal products are most effective and what the most (cost)effective positioning is of these combination therapies.

The National Health Care Institute therefore advises you, in light of the pilot and in the interest of the treatment of patients with multiple myeloma, to temporarily remove these combination therapies from the lock procedure, and to admit them to the health care package, pending the indication-wide advice. This will allow the professional group to achieve the most optimal (=(cost)effective) treatment for the patient during the pilot phase. We advise you to enter into price negotiations in this context. The National Health Care Institute considers a keen price negotiation justified, because

- the final positioning in the treatment algorithm, and thus the effectiveness in practice, is still unknown;
- there is still considerable uncertainty about the cost-effectiveness of the medicinal products/treatment combinations;
- there are indication extensions, or the medicinal products already had a position in the treatment algorithm, which have already largely recouped the research and development costs;

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- Other treatment options are already available for this condition.

We realise that the usual starting points for the price negotiations are missing, as the budget impact and the cost-effectiveness of the above combinations have not been determined. One option is to use the price negotiation to stop increasing the macro costs of treating myeloma during the pilot phase and to opt to freeze spending in a given year. The National Health Care Institute has made a global assessment of (the development of) the budget devoted to the pharmaco-therapeutic treatment of patients with multiple myeloma. This amounts to €123 million in 2017, €174 million in 2018 and €248 million in 2019. At the moment, most costs are made for lenalidomide and daratumumab, which occur in various combinations. Of the six combinations to be assessed, five consist of one of these two medicinal products, and one consists of the combination of lenalidomide and daratumumab. With regard to the negotiations with the various manufacturers, the National Health Care Institute notes that it is recommended that a financial investment for data registries and appropriate use ('gepast gebruik') research needs to be included.

Setting up a task force and data collection for the pilot
As explained above, the National Health Care Institute does not consider the assessment of individual treatment combinations in a particular treatment line to be the right instrument to address the package issues surrounding the affordability and positioning of the treatments indicated for multiple myeloma. To develop an alternative, indication-wide approach to our advisory process on the use of medicinal products for multiple myeloma, the National Health Care Institute will set up a Multiple Myeloma task force that represents all stakeholders. This approach aligns to the project 'Toekomstbestendig pakketbeheer' initiated by the National Health Care Institute to review our assessment system with regard to new developments. Patient organisations NFK and Hematon, and the professional group (HOVON's multiple myeloma working group) have already indicated that they are in favour of this alternative approach. The manufacturers involved also want to cooperate.
The alternative approach requires understanding of the use and benefits of treatments in Dutch practice. This requires disease-specific and independent data collection. Within the National Health Care Institute's 'Regie op Registers' project, which seeks to develop reliable registries for expensive medicinal products for package management and appropriate use, multiple myeloma will be included as one of the case studies.

In the context of this alternative approach, the National Health Care Institute also sees a major role for further studying the appropriate use of drugs. In this context, we would like to draw your attention to the professional group's initiative, which proposes an investigation of the duration of treatment of daratumumab-lenalidomide-dexamethasone, a combination that each patient, as expected by the professional group, will eventually receive during the treatment process. This can potentially lead to significant cost savings. We recommend that adequate financial resources be made available for the pilot, data collection and appropriate use research.

Timeline
The National Health Care Institute estimates that the development of this alternative approach will take up to a maximum of 2.5 years. This means that we

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also advise you to include new medicinal products (combinations) in the pilot that meet the criteria for the lock procedure during the preparation of this new approach, after a positive advice from the National Health Care Institute, in coordination with the task force, temporarily, subject to condition, and after keen price negotiations.

The National Health Care Institute would like to point out that in the future this alternative, innovative, indication-wide approach may become more common, particularly where the dynamics of the treatment landscape are great and the positioning of various (new) medicinal products is uncertain. At the moment we are noticing this particularly in haematological oncology, for instance in the treatment of chronic lymphatic leukaemia.

Preliminary advice

Considering all this and based on the special nature of the multiple myeloma indication, the National Health Care Institute advises you, in the context of a pilot, to temporarily include the above combination therapies in the health care package, under conditions and following keen price negotiations, pending a definitive approach and advice from the National Health Care Institute. It is in the interest of patients with multiple myeloma that the combination therapies that have been mentioned become available. The National Health Care Institute will set up a Multiple Myeloma task force, in which the stakeholders are represented. In this task force, we will work together to develop an alternative approach to our advisory process on the use of medicinal products for multiple myeloma. Real-time monitoring and appropriate use research will be given an important focus.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

Annex: ACP advice on multiple myeloma