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2024044330

Our reference
2024044330

Date 16 January 2025
Re: Advice lock procedure medicinal product daratumumab (Darzalex®) for the treatment of AL amyloidosis.

Dear Ms Agema,

The National Health Care Institute advises you on the assessment of daratumumab (Darzalex®) for the treatment of AL amyloidosis. The reason for this advice was the placement of daratumumab in the lock procedure for expensive medicinal products.

Registered indication
Daratumumab (Darzalex®) in combination with cyclophosphamide, bortezomib and dexamethasone is indicated for the treatment of adult patients with newly diagnosed systemic free light chain (Amyloid Light Chain, AL) amyloidosis.

AL amyloidosis is a disease with a build-up of improperly folded proteins, which start to clot together and then form amyloid fibres. The deposition and build-up of these amyloid fibres in the tissues of vital organs, such as the heart, kidneys, liver and nerves, progressively damage them.

Claim by the marketing authorisation holder
Daratumumab (Darzalex®) in combination with bortezomib, cyclophosphamide and dexamethasone (Dara+CyBorD) has a therapeutic value over bortezomib, cyclophosphamide and dexamethasone (CyBorD) alone for the above indication.

Package advice
The National Health Care Institute advises you not to include daratumumab for AL amyloidosis in the basic health care package.
The National Health Care Institute finds that daratumumab meets the legal criterion of 'established medical science and medical practice' and that there is an added value compared to the treatment with CyBorD alone. However, the cost-effectiveness analysis provided by the marketing authorisation holder is of insufficient quality. The results cannot be used in the decision-making. The National Health Care Institute is therefore unable to determine the cost-effectiveness or to advise on any price negotiations. This is essential for you and for the National Health Care Institute because the reimbursement of daratumumab at the marketing authorisation holder’s current asking price might lead to a treatment that would not be cost-effective. In addition, the high price, combined with the number of patients, leads to a budget impact that can only be

considered socially responsible if the treatment is cost-effective. The National Health Care Institute is aware that the outcome of the National Health Care Institute's assessment will be disappointing both for patients and practitioners. The National Health Care Institute therefore invites the marketing authorisation holder to modify the pharmaco-economic analysis.

We explain the preparation of this package advice below.

General

At your request, the National Health Care Institute assesses whether care should be part of the standard health insurance package from the perspective of the basic healthcare package paid from joint premiums.

The National Health Care Institute assesses on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity[4] and feasibility[5]. The Scientific Advisory Board (WAR) has advised the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. Stakeholders were consulted during the process.

Comprehensive weighting of package criteria

Effectiveness

Established medical science and medical practice

The treatment of AL amyloidosis is described in the 2020 guideline 'Treatment of systemic AL amyloidosis'. The treatment goal is to achieve a rapid and deep haematological response as this provides the best prognosis. No pharmacological treatment is currently registered and being reimbursed specifically for AL amyloidosis; its treatment is therefore based on antiplasma cell-focused therapy as used for the treatment of multiple myeloma.

The patient's condition at diagnosis determines the treatment. Patients who are fit to undergo autologous stem cell transplantation (ASCT) are first subjected to a cyclophosphamide, bortezomib and dexamethasone (CyBorD) regimen, followed by high doses of melphalan (HDM) and ASCT. However, most patients are not well enough for ASCT (~80%) and receive standard treatment with CyBorD. This treatment will be evaluated for effectiveness after the first 3 months, and a choice will be made whether to continue treatment or to initiate secondary care treatment. This is important because if the treatment is not responding adequately, it will be necessary to switch to an alternative treatment in time to prevent further amyloid build-up and subsequent organ damage. At present, daratumumab is one of the secondary care treatments for AL amyloidosis.
In the controlled, open-label phase 3 ANDROMEDA study, daratumumab was

[1] Real-world package management 4 (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[2] Assessment of the established medical science and medical practice (2023). National Health Care Institute. Via www.zorginstituutnederland.nl.

[3] Healthcare Cost-Effectiveness Assessment Framework Report (2024). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[4] Necessity is related to both the medical need due to the severity of a disease for the patient (burden of disease) and the need to insure something. See the report on real-world package management 4 (2023).

[5] The package criterion of feasibility deals with whether it is feasible or sustainable to include a specific form of care in the basic health care package. It is therefore mainly a test of a number of implementation aspects, such as the health care organisation, the support base, ethical and legal aspects, budget impact, etc. See the report on real-world package management 4 (2023).

studied as primary care treatment in combination with standard CyBorD treatment, and compared with standard CyBorD treatment. The professional association sees a place for daratumumab in combination with CyBorD as a primary care treatment for AL amyloidosis, replacing the current standard treatment of CyBorD alone. The revision of the Dutch AL amyloidosis guideline is currently under way. The HOVON multiple myeloma working group indicated that in this revised version of the daratumumab + CyBorD guideline, primary care treatment will be preferred for adults with newly diagnosed systemic AL amyloidosis.

Adding daratumumab to the current standard CyBorD therapy results in an increase in the number of patients with complete haematological response. In the study, 18.1% in the control arm and 53.3% in the intervention arm had a complete haematological response. In addition, the percentage of patients with cardiac and renal response increased. This has a predictive value for the probability of death. The data for overall survival (OS) is as yet immature. There is no evidence that adding daratumumab to CyBorD results in a clinically relevant change in the quality of life during the first 24 weeks of treatment.

Despite the lack of some crucial long-term effects, the National Health Care Institute concludes that adding daratumumab to standard CyBorD treatment in adults with newly diagnosed AL amyloidosis has an added value compared to CyBorD alone because of the extensive positive effects on complete haematological response and organ response, and the positive correlation of haematological response and organ response with overall survival.

Daratumumab, in combination with bortezomib, cyclophosphamide and dexamethasone for the treatment of adult patients with newly diagnosed systemic AL amyloidosis is therefore in line with the current established medical science and medical practice.

Budget impact analysis
The National Health Care Institute estimates that 199 patients per year will be treated with daratumumab + CyBorD for this indication in year 3 after inclusion in the package. The total costs per patient per year are €131,847. This results in possible macro costs of €13.3 million in the third year. When substitution is also taken into account, the budget impact in year 3 amounts to €12.5 million.

Cost-effectiveness
The cost-effectiveness analysis provided by the marketing authorisation holder is of insufficient quality. As a result, the National Health Care Institute cannot provide a methodologically reliable estimate of the cost-effectiveness.
In particular, the difference in survival between the ANDROMEDA study and the marketing authorisation holder model carries significant weight in this matter. The results of the economic model differ from the latest data from the ANDROMEDA study. The ANDROMEDA study shows a 5-year survival rate that is up to 20% higher than estimated in the model – this applies to both treatment arms. On the basis of the model, the National Health Care Institute cannot determine what effect this could have on the incremental cost-effectiveness ratio (ICER[6]).

[6] The ratio between the differences in costs and effects is called the incremental cost effectiveness ratio (ICER). The effects of the treatment are expressed in QALYs. This stands for Quality Adjusted Life Years, which means: one year of good quality life gained. We calculate the number of QALYs by multiplying the number of

In addition, daratumumab is already used in secondary healthcare in Dutch treatment practice. This standard treatment is not taken into account properly in the model. As a result, the survival ratio may be underestimated in the comparison arm, which may result in an over-optimistic ICER.

The National Health Care Institute takes the view that a new model should be developed in which survival is primarily based on the results of the ANDROMEDA study. The final analysis of the ANDROMEDA study has since been carried out and these data provide a good basis for setting up a new model.

Should you need any further information, please do not hesitate to contact us. The pharmacotherapeutic report, pharmaco-economic report and the budget impact analysis are attached to this letter.

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board

years of life of the patient by the average quality of life as far as it is related to health. The QALY allows us to compare the cost-effectiveness of different types of treatments for different types of conditions. Healthcare Cost-Effectiveness Assessment Framework Report (2024). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.