Zorginstituut Nederland

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National Health Care Institute
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Our reference
2023004477

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Date 13 December 2023
RE: Advisory report lock procedure medicinal product abemaciclib (Verzenios®) for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence.

Dear Mr Kuipers,

The National Health Care Institute is hereby sending you the package advice for abemaciclib (Verzenios®) for the treatment of 'hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence'. The reason for this advice was the placement of abemaciclib in the lock procedure for expensive medicinal products.

Registered indication
Abemaciclib, in combination with endocrine therapy, is indicated for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence.

Claim by the marketing authorisation holder
For this indication, the MAH is claiming a therapeutic added value for abemaciclib (Verzenios®) compared to endocrine therapy alone.

Package advice
The National Health Care Institute recommends that abemaciclib <u>not</u> be included in the basic health care package for the indication HR-positive, HER2-negative, gland-positive early breast cancer with a high risk of recurrence. For this indication, abemaciclib does not meet the legal criterion for 'established medical science and medical practice'. The development of our package advice is explained below.

<u>General</u>
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

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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) advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. If there are risks regarding the accessibility and affordability, the assessment of the package criterion of effectiveness (established medical science and medical practice) will be placed in the wider societal context of the four package criteria. The Insured Package Advisory Committee (ACP) advises the Executive Board of the National Health Care Institute in this regard. This *appraisal* results in the package advice. Stakeholders are consulted during the process.

Since abemaciclib does not meet the legal criterion of 'the established medical science and medical practice' for the relevant indication, the full weighting of the four package criteria and advice from the ACP is not relevant in this case.

Effectiveness
Established medical science and medical practice
Patients with HR positive and HER2 negative early breast cancer with a high risk of recurrence have a 5-year recurrence risk of 22% despite standard treatment. In this particular patient population, there is still an unmet medical need for clinically more effective adjuvant treatment. In this context, abemaciclib added to adjuvant endocrine therapy, which is considered standard adjuvant treatment for the present indication, was studied in one direct comparative open-label, randomized phase III multicentre study (MonarchE). The primary endpoint was invasive disease-free survival (IDFS). Key secondary endpoints were overall survival (OS) and quality of life (QoL).

Based on the study results, the National Health Care Institute concludes that early treatment of HR+/HER2- breast cancer with abemaciclib added to standard endocrine therapy does not result in a statistically significant and clinically relevant effect on survival (OS). This conclusion is based on the outcome of a planned interim analysis over a median follow-up duration of 42 months (3.5 years) with a data maturity of 51% and a large number of events (a total of 330 events in both study arms). Due to this large number of events, as well as in line with the outcome of additional statistical analyses and validations carried out by the National Health Care Institute, a clinically relevant effect on OS during this follow-up period can even be excluded with a very high degree of certainty (97.5%). This applies to both the relative and the absolute effect difference. As is usual in the assessment of oncological medicinal products, the National Health Care Institute based its assessment on the PASKWIL criteria (2023) established by the commission for the assessment of oncological medicinal products

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

[2] Beoordeling Stand van de Wetenschap en Praktijk (2023). National Health Care Institute. Via www.zorginstituutnederland.nl.

[3] Rapport kosteneffectiviteit (2015). 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 health care organisation, support, ethical and legal aspects, budget impact and so on. See the report on real-world package management 4 (2023).

(cieBOM). These allow an assessment of the clinical relevance of the difference in survival rate after a median follow-up duration of at least 3 years for adjuvant treatments.

Based on the above, the National Health Care Institute concludes that there is high-quality evidence that OS does not increase by adding abemaciclib to endocrine therapy, compared to endocrine therapy alone. Since curation [i.e. survival (OS)] is considered the main treatment goal in the treatment of early breast cancer and the National Health Care Institute can assess the effect of abemaciclib on OS with sufficient scientific reliability to draw conclusions from it, extensive assessment of the effect of abemaciclib on IDFS (as a surrogate outcome parameter for OS) has no added value.

The quality of life of patients treated with abemaciclib in combination with endocrine therapy seems similar to that of patients treated with endocrine therapy alone, with the exception of the item "I have diarrhoea" (FACT-ES C5). This was significantly increased in the abemaciclib arm during the first 12 months of treatment.

In addition, treatment with abemaciclib is likely to result in a clinically relevant increased incidence of severe adverse effects, whether or not related to the study medication, and an increase in the number of discontinuations due to adverse events. Finally, abemaciclib has additional warnings and precautions for severe liver or kidney disorders, abnormal blood levels (neutropenia) or infections. It does have a similar ease of use to endocrine therapy.

All in all, the National Health Care Institute concludes that abemaciclib does not meet the established medical science and medical practice for the treatment of adult patients with HR-positive, HER2-negative, node-positive early breast cancer with a high risk of recurrence. The National Health Care Institute realises that patients with this type of breast cancer are unlikely to receive any treatment with abemaciclib in the Netherlands as a result. At the same time, the National Health Care Institute prevents patients from long-term use of a medicinal product that does not offer any prospect of cure but can adversely affect their quality of life. This serves both their personal and societal interests.

The National Health Care Institute is of course prepared to reconsider the package eligibility of abemaciclib for the specific indication if additional research data not previously assessed by the National Health Care Institute leads to scientific publications that justify this decision.

Should you need any further information, please do not hesitate to contact us. The pharmacotherapeutic report is attached.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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