Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

To the Minister of Health, Welfare and Sport
P.O. Box 20350
2500 THE HAGUE

Date 12 March 2025
Re: Package advice for the lock procedure medicinal product avapritinib (Ayvakyt®) for mast cell disease

Dear Ms Agema,

The National Health Care Institute advises you on the assessment of avapritinib (Ayvakyt®) for the treatment of certain patients with advanced systemic mastocytosis, or mast cell disease. This advice was prompted by the placement of avapritinib in the package lock for expensive medicinal products.

Condition
Mastocytosis is a rare blood disease. Due to a genetic abnormality, there is abnormal growth and accumulation of white blood cells. If the disease is in a later stage, it is referred to as advanced systemic mastocytosis. Organ damage occurs in these patients. There are three subtypes of the advanced systemic mastocytosis, namely aggressive systemic mastocytosis (ASM), systemic mastocytosis in combination with haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL). Advanced systemic mastocytosis remainsincurable, and is an aggressive, rare disease that causes premature death of patients. The median survival after diagnosis is between 2 and 41 months, depending on the subtype. In the Netherlands, an estimated 60 patients suffer from this disease. Patients are currently being treated with midostaurin, cladribine and (peg) interferon-a.

Registered indication
Avapritinib (Ayvakyt®) is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis in combination with haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), following at least one systemic therapy.

In addition, avapritinib is also registered for certain patients with gastrointestinal stromal tumours (GIST) and indolent systemic mastocytosis (ISM). Avapritinib is already being reimbursed for GIST. The ISM indication has only recently been registered and is not included in this assessment.

Claim by the marketing authorisation holder
Avapritinib (Ayvakyt®) has added value compared to standard/usual treatment for the registered indication.

Package advice

National Health Care Institute
Care
Medicinal Products

Date
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Our reference
2025005752

The National Health Care Institute has determined that avapritinib, when treating adult patients with ASM, SM-AHN or MCL, after at least one systemic therapy, meets the legal criterion of 'established medical science and medical practice' and that there is an added value compared to standard/usual treatment with midostaurin, cladribine and (peg) interferon-a. However, based on the available data, the cost-effectiveness is unfavourable. The National Health Care Institute recommends that avapritinib for the above indication be included in the basic health care package, provided that the price can be reduced by 75% after successful price negotiations. The National Health Care Institute advises you to take into account during price negotiations the indication extension of avapritinib to patients with ISM; this is a larger group of patients than the group of patients with advanced systemic mastocytosis.

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 health care 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) 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 societal weighting results in the package advice. Stakeholders are consulted during the process.

Comprehensive weighting of package criteria

Effectiveness

Established medical science and medical practice

Two single-arm studies (EXPLORER and PATHFINDER) have investigated avapritinib for patients with advanced systemic mastocytosis. Because there was no control arm in the study, the results were indirectly compared to a real-world control cohort with data from European and American patients with advanced systemic mastocytosis. After a follow-up of approximately 17 months, the patients in the study who received avapritinib had not yet achieved median survival compared to the 17.2-month median survival in the control cohort population treated with standard treatment. An unpublished analysis with a longer follow-up

[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] Cost-effectiveness report (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 the health care organisation, the support base, ethical and legal aspects, budget impact, etc. See the report on real-world package management 4 (2023).

of approximately 30 months shows that median survival in the avapritinib study has still not been achieved, while the median survival in the control cohort was 17.5 months. These results of the indirect comparison seem to indicate a clinically relevant survival benefit of avapritinib over standard treatment. When looking at disease activity, avapritinib also appears to provide a better response than standard treatment. Furthermore, treatment with avapritinib has been shown to provide (significant) clinically relevant improvement in quality of life. In addition, the adverse reaction profile of avapritinib appears to be more favourable than that of standard treatment.

Because the disease is very rare, the evidence for the different treatments already in use in Dutch medical practice is limited and the follow-up duration in the avapritinib studies is relatively short, the evidence is very low quality. Despite the uncertainties mentioned, the limited data suggest a clinically relevant effect of avapritinib on all key outcomes. Better research in the form of a direct comparative study between avapritinib and existing treatments does not seem possible due to the rarity of the disease and a back-against-the-wall situation.

The National Health Care Institute, advised by the Scientific Advisory Board (WAR), has concluded that avapritinib for the treatment of adult patients with ASM, SM-AHN or MCL after at least one systemic therapy has added value compared to standard/usual treatment with midostaurin, cladribine and (peg) interferon-a.

Cost-effectiveness
The cost-effectiveness analysis of the marketing authorisation holder is of sufficient quality and can be used for policy decision-making. The cost-effectiveness estimate is higher than the reference value considered relevant for this condition. Therefore, avapritinib is not a cost-effective intervention. The ICER reported by the marketing authorisation holder is €373,840/QALY. At a reference value of €80,000, the price of avapritinib would have to be reduced by at least 75% in order to be considered cost-effective care. In addition, the National Health Care Institute notes that there is still substantial uncertainty in the analysis about the maintenance of the long-term effect of avapritinib, the modelled health benefits achieved in patients who have discontinued avapritinib but remain progression-free, and the modelled utilities for patients with both progression-free and progressive disease.

Budget-impact analysis
The National Health Care Institute estimates that 19 patients per year will be treated with avapritinib for this indication in the third year after inclusion in the insured package. The total annual costs are calculated at €353,939.53 per patient. This results in macro costs of €5.8 million in the third year. When taking into account the substitution of midostaurin, cladribine and (peg) interferon-a, the budget impact in the third year will reach €5.6 million.

ACP advice (social weighting)
The commission sees the importance of avapritinib becoming available for the registered indication. This is only possible at a socially acceptable price. The commission recommends not to include avapritinib in the basic health care insurance for this indication unless a price reduction of 75% is negotiated. As this is a rare disease with a very small group of patients for the time being and it involves a small-scale medication manufacturer, the commission does not refer to

'at least' 75%. The indication extension of avapritinib should be taken into account when concluding the financial arrangement. The commission also believes that arrangements for appropriate use should be made to ensure that the medicinal product can be used correctly for patients with this serious condition.

The National Health Care Institute shall adopt the ACP advice.

Appropriate use
The National Health Care Institute underlines the importance of appropriate use of avapritinib. By formulating start and stop criteria, the use for appropriate patients can be ensured from secondary healthcare. Dose reduction could also be considered as an option, e.g. with long-term successful treatment. In addition, the National Health Care Institute takes the view that treatment with avapritinib should take place at centres of expertise. The National Health Care Institute will discuss with the professional association how the appropriate use of avapritinib can be applied in practice.

In conclusion, The National Health Care Institute recommends that you include avapritinib in the health insurance package for the above indication, provided that the price can be reduced by 75% after successful price negotiations.

Should you need any further information, please do not hesitate to contact us. The assessment reports have been added as annexes (pharmacotherapeutic report, budget-impact analysis, pharmaco-economic report).

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board

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