



> Return address PO Box 320, 1110 AH Diemen

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

Date 16 January 2025
Re: Package advice lock procedure for medicinal product ripretinib
(Qinlock®)

Dear Ms Agema,

The National Health Care Institute hereby advises you on the outcome of its assessment of ripretinib (Qinlock®) for the treatment of advanced gastrointestinal stromal tumour (GIST). The reason for this advice was the placement of ripretinib in the lock procedure for expensive medicinal products.

GIST is a rare tumour in the gastrointestinal tract. It can occur throughout the gastrointestinal tract but is found mainly in the stomach (50-60%) and small intestine (20-30%). The severity of the disease varies per patient and depends in particular on the size of the tumour. In 85% of patients, the primary GIST can be surgically removed. However, in 50% of cases, the tumour reoccurs. International guidelines therefore recommend standard (adjuvant) treatment with imatinib following surgical removal of the tumour. Sunitinib, regorafenib and ripretinib, respectively, are used for the secondary, third-line and fourth-line treatment of advanced GIST. This approach is in line with the current treatment advice of the Dutch physicians' association.

Registered indication

Ripretinib is registered for the treatment of adult patients with advanced GIST who have previously been treated with three or more kinase inhibitors, including imatinib.

Claim by the marketing authorisation holder

Addition of ripretinib to the standard of care (SoC) treatment algorithm for GIST has a therapeutic added value over the SoC treatment algorithm for the treatment of adult patients with advanced GIST who have previously been treated with three or more kinase inhibitors, including at least imatinib.

Package advice

The National Health Care Institute advises you not to include ripretinib in the basic health care package for the treatment of advanced GIST. Although the National Health Care Institute has determined that ripretinib meets the legal criterion of 'established medical science and medical practice' for this indication, the National Health Care Institute cannot make a valid and reliable statement about its cost-effectiveness. The pharmacoeconomic analysis is of insufficient quality to reliably use its results in decision-making. The National Health Care Institute realizes that the outcome of this assessment is disappointing for patients with GIST and their practitioners. The National Health Care Institute therefore requested the marketing authorisation holder to provide the missing scenario analyses and essential data as soon as possible.

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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 criteria¹, effectiveness², cost-effectiveness³, necessity⁴ and feasibility⁵. The Scientific Advisory Board (WAR) advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. Stakeholders are consulted during the process.

Comprehensive weighting of package criteria

Effectiveness

Established medical science and medical practice.

The effectiveness and safety of ripretinib were investigated in a multicentre, double-blind, placebo-controlled phase-three study (INVICTUS study). This study included 129 patients, 85 of whom received ripretinib and 44 received placebo. Median overall survival (OS) in the ripretinib arm was clinically relevant longer than in the placebo arm (15.1 versus 6.6 months). The relative effect estimate was also clinically relevant. There may have been a clinically relevant difference in the quality of life outcome between the ripretinib and placebo arms. However, treatment may have been associated with clinically relevant more intervention-related serious adverse effects and clinically relevant more discontinuations due to adverse effects.

Compared to the minimal clinically important difference, the PASKWIL criteria of the physicians' association for palliative treatment, the effect on OS in absolute

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 Feasibility deals with whether it is feasible or sustainable to include a specific form of care in the basic health care package. It is 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).

and relative terms is clinically relevant. While confidence in the outcome OS is reduced by the short median duration of follow-up, a follow-up analysis shows that the median OS in the ripretinib arm is extending and in the placebo arm is slightly decreasing (18.2 versus 6.3 months, respectively). In addition, the effect on OS may be clouded by the high degree of cross-over. More than 67% of the placebo arm switched to ripretinib after progression. Nevertheless, the effect on OS remains clinically relevant, which increases confidence in the outcome measure OS. The National Health Care Institute therefore considers it plausible that treatment with ripretinib in Dutch practice will lead to a clinically relevant prolongation of survival. Confidence in the quality of life outcome remains low due to the short follow-up duration and the risk of bias. The same applies to the adverse effects outcome. However, given the good treatability of the adverse effects of ripretinib, the National Health Care Institute, supported by its Scientific Advisory Board (WAR), concludes that, all in all, the beneficial effects of the treatment outweigh the adverse effects. For this indication, ripretinib meets the legal criterion for 'established medical science and medical practice'.

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Cost-effectiveness

The marketing authorisation holder has not provided essential information and available data, which are necessary for a methodologically reliable estimation of cost-effectiveness, even after an explicit written request from the National Health Care Institute. In addition, specific additional analyses requested by the National Health Care Institute were not carried out by the marketing authorisation holder, preventing the identification of the impact of certain factors on cost-effectiveness. As a result, the pharmacoeconomic analysis is insufficiently transparent and shows a lack of quality and representativeness. Therefore, a scientifically valid and reliable statement on the cost-effectiveness of ripretinib for the present indication is not possible. As such, the National Health Care Institute cannot reliably advise you regarding any price negotiations.

Budget impact analysis

The National Health Care Institute expects 25 GIST patients to start ripretinib in the fourth treatment line in the third year after market introduction. The costs per patient are €164,660 if ripretinib is discontinued on progression. If ripretinib is continued after progression, the expenditure for ripretinib once daily and twice daily increases by €84,684 and €212,329 per patient, respectively. The National Health Care Institute considers it likely that continued treatment after progression is likely to occur once daily in 20% of patients. In year 3, the budget impact for ripretinib would be €4.5 million.

In particular, there is uncertainty about the number of patients that will move from the third line to the fourth line, and about the growth in the number of patients, respectively. The effect on the budget impact could go in either direction. In addition, there is uncertainty about the treatment duration of ripretinib. In the INVICTUS study, 21% continued treatment after progression. 54% received an increased dose of ripretinib. Although this dose increase is off-label, the physicians' association takes the view that this also appears to be a real option in Dutch clinical practice for patients with GIST who would otherwise not have any treatment options left. Continued treatment after progression including dose increase as estimated by the professional association (20%) has been clarified in a scenario analysis. The budget impact then increases by about €1.0 million compared to the base case. The percentage of patients who will receive a

dose increase estimated by the physicians' association is lower than in the INVICTUS study.

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, pharmacoeconomic report).

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board

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