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To the Minister of Health, Welfare and Sport
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2025023530

Date 17 October 2025
Re: Package advice lock procedure medicinal product ripretinib (Qinlock®) for gastrointestinal stromal tumour (GIST)

National Health Care Institute

Research, Development and Medicinal Products
Medicinal Products Team

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Contact

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Our reference

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Dear Mr Bruijn,

The National Health Care Institute advises you on the outcome of the 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. The National Health Care Institute advises you to include ripretinib in the basic healthcare package for this indication.

GIST is a rare tumour that can occur throughout the gastrointestinal tract, but is found mainly in the stomach (50-60%) and small intestine (20-30%). The severity of this varies from patient to patient and depends mainly on the size of the tumour. In 85% of patients, a primary GIST is surgically removable. In 50% of the cases, the disease recurs. International guidelines therefore recommend standard (adjuvant) treatment with imatinib following surgical removal of the tumour. If the disease can no longer be adequately treated with that, imatinib is replaced by sunitinib, regorafenib and ripretinib, respectively. This approach is in line with the current treatment advice of the Dutch physicians' association. In 2023, 492 new patients in the Netherlands were diagnosed with GIST. Most of them are over 50 years old. At that time, there were a total of 1854 GIST patients.

Licensed indication

Ripretinib is indicated 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

The addition of ripretinib to the standard of care (SoC) for GIST has added value compared to SoC only for the treatment of adult patients with advanced GIST who have previously been treated with three or more kinase inhibitors, including at least imatinib.

Background

On 16 January 2025, The National Health Care Institute advised your predecessor not to include ripretinib in the health insurance package for the treatment of

advanced GIST. Although ripretinib met the legal criterion of 'the established medical science and medical practice', the National Health Care Institute was unable to make a valid and reliable statement about its cost-effectiveness. The pharmaco-economic analysis was of insufficient quality to use the results confidently in decision-making. As a result, the National Health Care Institute was unable to issue a transparent advice for a possible price negotiation.

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Package advice

Based on an improved cost-effectiveness analysis by the marketing authorisation holder, the National Health Care Institute has carried out a reassessment. Supported by the Scientific Advisory Board (WAR), it has been established that it is now of sufficient quality for decision-making. The National Health Care Institute advises you to include ripretinib in the health insurance package for the registered indication, provided that a price reduction of at least 75% can be agreed with the marketing authorisation holder.

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 health insurance package paid from joint premiums. The National Health Care Institute makes its assessments on the basis of 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. 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 social context of the four package criteria. The Insured Package Advisory Committee (hereinafter also "ACP") advises the Executive Board of the National Health Care Institute in this regard. This social weighting results in the package advice. Stakeholders are consulted during the process.

Comprehensive weighting of package criteria

Effectiveness

Established medical science and medical practice

In January 2025, following advice from the WAR, the National Health Care Institute had already ruled that ripretinib complies with the established medical science and medical practice for the indicated indication.⁶The effectiveness and safety of ripretinib were investigated in a multicentre, double-blind, placebo-

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: 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 healthcare package. It is therefore primarily a test of implementation aspects such as the care organisation, support base, ethical and legal aspects, budget impact and so on. See: Real-world package management 4 (2023).

⁶ See <https://www.zorginstituutnederland.nl/documenten/2025/01/16/pakketadvies-sluisgeneesmiddelripretinib-ginlock>

controlled phase-3 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. In terms of the quality of life outcome, there may have been a clinically relevant difference between the ripretinib and placebo arms. However, the treatment may have been associated with clinically relevant more intervention-related, serious adverse effects and clinically relevant more discontinuations due to adverse effects.

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Compared to the minimal clinically important difference, the PASKWIL criteria of the physicians' association for palliative treatment, the effect on OS in absolute and relative terms is clinically relevant. While confidence in the OS outcome parameter is reduced by the short median follow-up duration, a follow-up analysis shows that the median OS in the ripretinib arm is getting longer, and in the placebo arm slightly shorter (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 switches 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 likely that treatment with ripretinib will lead to clinically relevant prolongation of the OS in Dutch practice. 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 the Scientific Advisory Board (WAR), concludes that, overall, 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'.

Cost-effectiveness

In the first cost-effectiveness assessment in January 2025, the lack of specific information prevented a methodologically reliable analysis on key issues. As a result, the National Health Care Institute was unable to give a solid and transparent advice for a possible price negotiation. The marketing authorisation holder has since provided this information. The cost-effectiveness analysis has now been improved in these areas in such a way that, according to the National Health Care Institute, supported by the WAR, the results can be used for decision-making. The cost-effectiveness estimate is above the reference value of €80,000 that is considered relevant for this condition. The ICER is €272,992/QALY. Ripretinib is therefore not a cost-effective intervention. With a reference value of €80,000, the price of ripretinib should decrease by 75% to be cost-effective. Because this calculation is based on the results of the phase-3 study (INVICTUS) and not on the probable clinical use of ripretinib by Dutch physicians, there is uncertainty about the ICER if the same dose is continued with disease progression, and not a double dose, and how this dosing regimen affects the overall treatment duration and survival outcome.

Budget impact analysis

The National Health Care Institute expects 25 GIST patients to start on ripretinib in the fourth treatment line in the third year following market introduction. The cost per patient is €164,660 if ripretinib is discontinued on progression. If ripretinib is continued after progression, the costs for ripretinib once daily and

twice daily increase by €84,684 and €212,329 per patient, respectively. Based on the study, the National Health Care Institute considers it likely that continued treatment after progression will occur only once a day 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, according to the physicians' association, during the initial assessment of ripretinib, this also appears to be a real option in Dutch clinical practice for patients with GIST who would otherwise not have another treatment option.⁷ Continued treatment after progression, including dosage increase, as estimated by the physicians' association at the initial assessment (20% of patients)⁸ was assessed in a scenario analysis. This percentage is lower than in the INVICTUS study. This means an increase in budget impact of about €1.0 million compared to the base case.

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Social appraisal

Ripretinib for the treatment of GIST was placed in the lock procedure in 2021.⁹ The budget impact amounts to €4.5 million to €5.5 million in year 3 after inclusion in the health insurance package. This budget impact is lower than the lock procedure threshold value.¹⁰ Because the study shows that GIST patients with no more treatment options, who are subsequently treated with ripretinib, live for an average of 8.5 months longer, the National Health Care Institute considers it socially important that this medicinal product will now become available to patients as soon as possible. The National Health Care Institute assumes that, if disease progression also occurs with ripretinib treatment, patients can continue treatment if the physician considers this necessary. That treatment strategy has been established to comply with the established medical science and medical practice.¹¹ However, following the initial negative advice issued by the National Health Care Institute in January 2025, the physicians' association indicated that for cost reasons ripretinib would only be used until disease progression occurs. The National Health Care Institute takes into consideration that the effect of ripretinib on patient survival is unknown. Nor has it been established whether this treatment strategy complies with the established medical science and medical practice. Although the budget impact is relatively limited, the asking price per patient remains exceptionally high. Ripretinib can only be included in the health insurance package at a socially acceptable price. The asking price should decrease to a level where the cost-effectiveness of the treatment falls below the maximum reference value of €80,000 per QALY. The National Health Care Institute, supported by a majority of the ACP, considers that in the context of continued treatment after disease progression, this requires a reduction of at least 75% of the asking price.

⁷ See advice letter dated 16 January 2025 (ref. 2024045201); see also the Pharmacotherapeutic Report dated 19 December 2024, p. 18

⁸ Ditto.

⁹ Govt Gazette 7 December 2021

¹⁰ Art. 2.4a Healthcare Insurance Decree

¹¹ See advice letter dated 16 January 2025 (ref. 2024045201); see also the Pharmacotherapeutic Report dated 19 December 2024, p. 18

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

Yours sincerely,

K.C. Timm-van Ruitenburg
Member of the Executive Board

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