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National Health Care Institute
Care
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Our reference
2024002870

Date 1 March 2024
Re: Package advice upadacitinib (Rinvoq®) for Crohn's disease

Dear Ms Dijkstra,

The National Health Care Institute advises you on the assessment of upadacitinib (Rinvoq®) for the treatment of moderately to severely active Crohn's disease. The reason for this advice was the placement of upadacitinib in the lock procedure for expensive medicinal products.

Registered indication
Upadacitinib (Rinvoq®) is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have responded inadequately or have not responded, or who are intolerant to conventional treatment or a biological product.

Claim by the marketing authorisation holder
The marketing authorisation holder specifically requests reimbursement for a narrower indication, namely patients who have responded inadequately to, no longer respond to, or are intolerant to biological treatment, and claims an equivalent value to vedolizumab and ustekinumab.

Package advice
National Health Care Institute advises you to include upadacitinib (Rinvoq®), for the treatment of patients with moderately to severely active Crohn's disease who have responded inadequately, no longer respond, or are intolerant to biological treatment in the basic health care package, provided that the net price of upadacitinib treatment following successful price negotiations does not lead to additional costs compared to standard treatment with vedolizumab or ustekinumab.
The National Health Care Institute has established that upadacitinib for the above indication meets the legal criterion of 'established medical science and medical practice' and that there is an equal value compared to the current standard treatment.

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 care package.

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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. Stakeholders were consulted during the process.

Comprehensive weighting of package criteria

Established medical science and medical practice

Crohn's disease is characterised by inflammation of the intestines, with a varying pattern of flare-ups and quiet periods. The inflammation is caused by an uninhibited immune response against bacteria in the intestines. Untreated, these inflammations can affect several layers of the intestinal wall and adjacent organs. Patients suffer from abdominal pain and diarrhoea. Fatigue, weight loss and fever also occur. In some patients, inflammation leads to constrictions, fistula and abscesses in the abdomen. The quality of life of patients with Crohn's disease is lower than that of the general population. Crohn's disease affects 331 per 100,000 people.

Crohn's disease is currently being treated with topical corticosteroids, systemic corticosteroids and, in case of inadequate response, TNF-alpha inhibitors. If patients also fail to respond adequately to TNF-alpha inhibitors, ustekinumab or vedolizumab is recommended. All these medical management treatments with different mechanisms of action are intended to induce and maintain disease remission.

Upadacitinib is a Janus Kinase (JAK) inhibitor. Ustekinumab and vedolizumab have a registered indication similar to upadacitinib. Both products have a similar place in the guidelines, in this case after an inadequate response to TNF-alpha inhibitor treatment. The professional group confirmed that upadacitinib has a similar place in the treatment of Crohn's disease, namely after an inadequate response to TNF-alpha inhibitors. The National Health Care Institute therefore considers these products as comparable treatments.

The evidence for the assessment of upadacitinib comes from the registration studies U-EXCEED, U-EXCEL and U-ENDURE. Upadacitinib was shown to be effective, compared to placebo, in inducing and maintaining both clinical and endoscopic remission.
In addition, a published network meta-analysis (NMA) has been used that included studies of, among others, upadacitinib, vedolizumab and ustekinumab, and compared them for the clinical remission endpoint. Based on the outcomes, the National Health Care Institute concludes that there are no clinically relevant differences between upadacitinib and ustekinumab and between upadacitinib and

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

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vedolizumab in achieving and maintaining clinical remission. In terms of adverse effects, the adverse effects profile of upadacitinib is similar to those of ustekinumab and vedolizumab. However, the potentially increased risk of malignancies, a major adverse cardiovascular event (MACE) and serious infections observed as a group effect with the JAK inhibitors should be considered. Caution is recommended in patients aged over 65 years, and patients already at increased risk of MACE and malignancies.

All in all, the treatment with upadacitinib complies with established medical science and medical practice. Based on the available data, upadacitinib has an equal value to ustekinumab and vedolizumab.

Budget impact analysis
The National Health Care Institute estimates that with a market penetration of 22.5%, 1391 patients per year will be treated with upadacitinib for this indication in year 3 after inclusion in the package.
The total costs per patient per year depend on the percentage of patients who receive a 15 or 30 mg maintenance dose after induction. The National Health Care Institute has therefore calculated two scenarios; scenario 1 where 75% of patients receive the higher dose of 30 mg as maintenance dose after induction. Scenario 2 where 50% receive the higher dose of 30 mg after induction. In addition, there should be a cost distinction made between the start year and a maintenance year.
The total costs per patient per year are between €20,136 and €22,114 for a start year (scenarios 2 and 1, respectively), and between €16,176 and €18,891 for a maintenance year (scenarios 2 and 1, respectively). This results in possible macro costs between €24.1 and €27.6 million (scenarios 2 and 1, respectively) in the third year. When substitution of ustekinumab and vedolizumab is taken into account, the budget impact in year 3 ranges from €2.8 to €6.3 million.

There is uncertainty about the percentage of patients who will receive the lower or higher dose of upadacitinib. In addition, there is uncertainty about the number of patients eligible for treatment after a TNF-alpha inhibitor and about the market penetration of upadacitinib.
Hospitals may purchase both vedolizumab and ustekinumab at a price lower than the pharmacy purchase price (AIP). In the budget impact analysis, this may lead to an underestimation of the actual additional costs of upadacitinib based on the list price.

Cost-effectiveness
Due to its equal therapeutic value, the National Health Care Institute has not assessed its cost-effectiveness.

The National Health Care Institute stresses that when upadacitinib is introduced to the health care package, there should be no additional costs due to the equal value of vedolizumab and ustekinumab. In conclusion, the National Health Care Institute notes that the patent for ustekinumab will expire in July 2024, which means that ustekinumab biosimilars are expected to enter the market and are likely to initiate a price decrease.

Should you need any further information, please do not hesitate to contact us.
The assessment reports have been added as annexes (pharmacotherapeutic

report and budget impact analysis).

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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