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Our reference
2024012007

Date 25 April 2024
Re: Package advice lock procedure medicinal product selumetinib (Koselugo®)

Dear Ms Dijkstra,

The National Health Care Institute advises you about the assessment of selumetinib (Koselugo®) for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above. The reason for this advice was the placement of selumetinib in the lock procedure for expensive medicinal products.

Registered indication
Selumetinib as monotherapy is indicated for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above.

Claim by the marketing authorisation holder
For the registered indication, selumetinib has added value compared to best supportive care by itself.

Package advice
The National Health Care Institute has determined that selumetinib meets the legal criterion of 'established medical science and medical practice' for the indication mentioned. However, based on the available data, the cost-effectiveness is unfavourable.
After being advised by the Insured Package Advisory Committee (ACP), the National Health Care Institute advises you to include selumetinib in the basic health care package for the above indication, provided that a price reduction of at least 84% is achieved. In addition, an orphan drug arrangement is also considered necessary. This should include agreements on start and stop criteria, the role of centres of expertise, the setting up of an indication committee, data collection (on at least the effect on tumour size, complications due to disease progression, safety and quality of life) and on evaluation moments. The professional group has already started drafting this.

If more founded evidence of the effects becomes available in the near future, the National Health Care Institute will be able to examine, in the context of cyclical package management, whether these lead to other conclusions at that time.

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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 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 (scientific weighting). 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 (societal weighting) results in the package advice. Stakeholders are consulted during the process.

Comprehensive weighting of package criteria
Scientific weighting
Established medical science and medical practice
Neurofibromatosis type 1 (NF1) is a dominant hereditary disorder. Due to a mutation in the NF1 gene, the body does not produce enough or not properly functioning neurofibromin in the body cells. This can eventually lead to uninhibited cell growth and, as a result, creates a higher risk of developing benign and malignant tumours. Selumetinib attacks plexiform neurofibromas (PN), a form of benign tumours. These are larger benign tumours that originate from larger nerves or from nerve networks.
In almost all people with NF1 (>99%), benign tumours form from the neural cells in the skin and brain, but also in other parts of the body. These tumours are called neurofibromas. They can take complex and large forms and are characterised by uncontrolled and unpredictable growth, with periods of rapid growth and periods of inactivity.
PN grow fastest in children, while the growth rate levels off in adult patients. PN can push on tissue as they grow. Depending on the location of the PN, this can cause various symptoms, such as pain, body deformity or disability. PN only shrink spontaneously in rare cases. Therefore, the symptoms will remain throughout the patients' life. In addition, the tumour can change from benign to

[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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malignant. This happens in 8 to 13% of cases. This type of cancer is called malignant peripheral nerve sheath tumour (MPNST).
NF1 is associated with a reduced life expectancy of 8 to 15 years, mainly due to malignant neoplasms and cardiovascular causes.

The efficacy of selumetinib was studied in a multicentre, uncontrolled, *open-label* Phase 2 study (SPRINT Phase 2) with a follow-up of 2.8 years (first data cut-off). 50 patients with at least one complication related to a plexiform neurofibroma were included. Selumetinib has been compared with best supportive care. For one outcome, progression-free survival (PFS), data from a historical control was available. For the other outcomes, the patient was its own control.
Because the symptoms related to PN differ between patients, it is difficult to demonstrate clinically relevant symptom reduction at group level. Therefore, in this specific dossier, the National Health Care Institute has assumed tumour size as a surrogate for reduction or worsening of symptoms. At group level, selumetinib has been shown to result in ≥20% shrinkage of symptomatic, inoperable PN in 40 to 66% of patients. Clinical experts also agree that this situation is rare in cases of a natural disease progression. Growth also decreased compared to a historical control group, since the PFS showed clinically relevant improvement. In patients with stable or growing PN, the trend is that their symptoms remain stable or worsen over time. Therefore, without a volume decrease of the PN, it is unlikely that the symptoms will decrease. The tumour shrinkage is therefore considered a clinically relevant effect in this severe, rare and heterogeneous disease for which no other registered treatment option is available that affects the cause of the disease. However, the effects are very uncertain due to the single arm study design, circumstantial outcome parameters and the outcome parameter PFS which is difficult to interpret for this indication. Quality of life at group level remained at least the same compared to the baseline, and clinically relevant improvement in quality of life was demonstrated in 38% to 53% of patients. The effects are also very uncertain for this outcome. Selumetinib results in adverse effects in almost all users. Twelve percent of patients in the study experienced an intervention-related serious adverse effect. Most adverse effects were manageable by dose interruption and dose reduction with or without additional intervention to manage the adverse effects. As a result, patients are able to take selumetinib for long periods of time, which implies that the adverse effects can be managed well for most patients. In addition, no adverse effect was life-threatening or fatal. Ten percent of patients permanently discontinued treatment because of an adverse effect.

Because of the promising results in the previous SPRINT Phase 1 study, patient and clinical equipoise, the small indication area and the back-against-the-wall situation, the choice for the uncontrolled study design is understandable. However, this poses a serious risk of bias and makes the effects uncertain in advance.

The National Health Care Institute concludes that the study results of selumetinib, such as tumour shrinkage, are promising, but that it remains uncertain whether selumetinib ultimately leads to symptom reduction at group level. The added value of selumetinib varies from patient to patient. At a patient level, clinically relevant improvements such as pain reduction and quality of life have already been demonstrated in the short term. The professional association therefore has an important role to play in the appropriate use of selumetinib.

Cost-effectiveness
The cost-effectiveness analysis of the marketing authorisation holder is of sufficient quality and can be used for decision-making.

However, the National Health Care Institute does not consider it realistic to rely solely on the ICER reported by the marketing authorisation holder (€170,774), because it is not clear what the quality of life of these patients is. In addition, there is no evidence for remaining progression-free in 55% of selumetinib-treated patients after the age of 24 for the remainder of their lives. Because of these uncertainties, the National Health Care Institute chooses to present two scenarios in the final conclusion of the scientific weighting. Scenario A would be the most realistic scenario when there is sufficient evidence for life-long progression-free survival of a large proportion of patients treated. Scenario B represents a more conservative scenario in which a less optimistic progression-free disease is assumed in the long term.

The cost-effectiveness estimation far exceeds the reference value considered relevant to this disorder, and selumetinib is therefore not a cost-effective intervention. The ICER ranges from €170,774 per QALY in scenario A to €332,319 per QALY in scenario B. At a reference value of €50,000, the price of selumetinib should be lowered by 70% to 84% to be cost-effective.

Many uncertainties have been studied through these scenarios, but not all of them. Amongst other things, the progression rate and the stabilisation of tumour growth after the age of 24 years are uncertain. There is also uncertainty about the assumptions about the course of the disease at best supportive care and the quality of life of patients who are progression-free. However, the National Health Care Institute considers that the above scenarios provide sufficient insight into the cost-effectiveness of selumetinib when influential assumptions change.

Budget impact analysis
Based on the calculations in the budget impact analysis, the National Health Care Institute expects between 39 and 114 patients to be eligible for selumetinib treatment in the third year following market introduction.
The total cost per patient for selumetinib depends on a patient's body surface area and can range from €89,129 to €297,125 per year. The total additional costs in the third year are between €6.8 and €19.9 million.

Societal weighting
Based on the scientific weighting, selumetinib meets the established medical science and medical practice, but there is great uncertainty about the effectiveness for the entire patient group. In addition, the product has been conditionally admitted to the market by the EMA due to limited safety data. So there are uncertainties about both effectiveness and safety.

In the ACP, the value of selumetinib has been weighted from a societal perspective. There is great uncertainty about the size and duration of effects on the crucial outcomes of 'symptom reduction' and 'quality of life'. Since the estimation of health benefits is mainly the result of extrapolations in the pharmaco-economic model, the estimation of cost-effectiveness is also very uncertain. In addition, there is uncertainty about the budget impact. This is an

innovative treatment for a patient group (children aged 3 years and older) for which there is currently no treatment available that addresses the underlying disease. Since these are children, the calculation of the burden of disease (and the corresponding reference value) may paint a too positive picture. These children lose a large number of QALYs (more than 35) compared to healthy children, mainly due to a lower quality of life. It is expected that the professional association will use this product appropriately. The formulation of start and stop criteria will ensure that this medicinal product will be used for the right patients and that it will be stopped if it proves not to be (sufficiently) effective. Due to the great uncertainty, the commission considers it important to include these arrangements in an orphan drug arrangement. In addition to start and stop criteria and an indication committee, data collection and evaluation are also important. In addition to tumour size and complications, better data on the effect of selumetinib on the quality of life are necessary. In the context of cyclical package management, the commission recommends to consider whether these future results (orphan drug arrangement and additional data from the MAH to the EMA) lead to different conclusions.

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,

Sjaak Wijma
Chairperson of the Executive Board

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