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Our reference
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Date 30 September 2020
Subject Package advice esketamine nasal spray (Spravato®)

Dear Ms van Ark,

Zorginstituut Nederland has completed the assessment of esketamine nasal spray (Spravato®) for the treatment of adults with treatment-resistant major depressive disorder. Based on this assessment, I recommend that you include esketamine nasal spray in the basic health care package, but as the 4th step of the treatment algorithm, after successful price negotiations, preferably in the form of *pay for performance* and/or *pay for proof* agreements.

I would like to explain our findings and final conclusion to you below.

General

You have placed esketamine nasal spray in the lock for expensive medicines for the indication mentioned above. From the point of view of the basic health care package paid from joint premiums, the Zorginstituut makes the assessment of whether new care should be part of the insured package. The guiding principle here is that people can trust that the available resources and capacity are spent wisely and carefully. For this reason, the Zorginstituut assesses how the care supply meets the public values of quality, accessibility and affordability: as well as the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. Only care that complies with this assessment will be reimbursed from the basic health care package. The Zorginstituut is advised by two independent committees: the Scientific Advisory Board (WAR) for the scientific and practical assessment of the data and the determination of the cost-effectiveness, and the Insured Package Advisory Committee (ACP) for the appraisal. We also consulted stakeholders during the assessment process.

Claim

Based on an earlier advice from the Zorginstituut regarding the framework for the claim, you have placed esketamine nasal spray (Spravato®) in the lock for expensive medicinal products. The Zorginstituut confirms its earlier advice that esketamine nasal spray falls under the demand for medical care referred to in

[1] Package management in practice 3 (2013). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[2] Assessment of established medical science and medical practice update (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[3] Cost-effectiveness in practice (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

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Article 2.4 of the Health Insurance Decree and is therefore not eligible for an assessment of inclusion in the Medicine Reimbursement System (GVS). Due to the special nature of the mental health care service (GGZ), consultations with stakeholders such as the Dutch Healthcare Authority (NZa) were initiated at an early stage. All efforts are aimed at ensuring that, in case of a positive package decision, esketamine nasal spray can be claimed by health care providers for reimbursement by health care insurers from 1 January 2021.

Introduction
The personal effects of depression can be profound. The condition has an impact on the quality of life and on a person's social and personal performance. The condition often leads to absenteeism and occupational disability, and can have a major impact on family life and social performance. 18.7% of all Dutch adults up to 65 years old have struggled with a depressive disorder at some point in their lives.
For the first time in a long while, a new medicinal product has been registered for this group of patients. Esketamine nasal spray is registered for the treatment of adults with a therapy-resistant major depressive disorder. The product is innovative because it uses a new mechanism of action which may also make it work faster than the existing medicinal products.

Integral package criteria weighting
Current level of established medical science and medical practice
In the 1st step of the pharmacotherapeutic treatment of depression, the patient can be started on various types of antidepressants. In the 2nd step, it is recommended to switch to another antidepressant mentioned in the 1st step. Given the registered indication and the Dutch guideline, esketamine nasal spray could be used as a 3rd step in the treatment. In the 3rd step, a second product is added to the antidepressant that proved to be insufficiently effective in the 2nd step (augmentation). At this point, esketamine nasal spray has a value comparable with that of the existing augmentation strategies.
Prior to the assessment, the occupational group indicated it foresaw a place later on in the treatment algorithm for esketamine nasal spray, namely in the 4th step, after non-response to at least three consecutive medical management steps with antidepressants and augmentation. Esketamine nasal spray has added value in this place in the treatment algorithm, compared to tranylcypromine.
The results of studies for esketamine nasal spray show various uncertainties, as do many other studies on medicinal products for depression. Nevertheless, esketamine nasal spray meets the established medical science and medical practice.

Budget impact
The annual treatment costs are €10,175 per patient. The augmentation strategies per patient amount to €20-€141 (including antidepressants) per year and tranylcypromine €2,435 per year.

The potential number of patients that will use esketamine nasal spray in the 3rd treatment step is very difficult to estimate. This could potentially be a very large patient group. The application of esketamine nasal spray in the third stage of treatment will lead to additional costs estimated at a minimum of €27.1 million and a maximum of €1.7 billion in the third year after inclusion in the package.
If esketamine nasal spray is used in the 4th treatment step, compared to

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tranylcypromine, the additional cost of esketamine nasal spray is estimated at €15.8 million after inclusion in the package.

Cost-effectiveness
In this case, a regular cost-effectiveness analysis is either not considered (in case of equal value compared to augmentation strategies) or not possible. The study results are not representative of the 4th step in the treatment algorithm for which added value has been established. In addition, there are very limited published data about tranylcypromine. In a very exceptional move, the Zorginstituut has created a cost-effectiveness signal. This enables the Zorginstituut to use the limited data to make a cautious assessment of the expected cost-effectiveness of the medicinal product, taking into account various assumptions. This cost-effectiveness signal has shown that esketamine is unlikely to be cost-effective in comparison to tranylcypromine.

Package advice – conclusion
For the first time in a long while, a new medicinal product has been registered for this group of patients. Esketamine nasal spray is innovative because it uses a new mechanism of action, which may also make it work faster than the existing medicinal products.
However, there are also many uncertainties about the place of the product, its effectiveness, budget impact and cost-effectiveness. In our advice to you, we therefore want to address these uncertainties.

The Zorginstituut sees an added value for esketamine nasal spray when the product is used in the 4th step of the treatment algorithm. This is in line with the advice of the occupational group. I am taking into consideration that the 3rd step of the treatment algorithm already has adequate treatment options. By legally limiting the use of this product to the 4th step, the risk of an extremely large budget impact (as described above for the use in the 3rd step) is greatly reduced.

I therefore recommend that you proceed to price negotiations and inclusion in the insured package at this time, but only in the 4th step of the treatment algorithm. I advise you to consider making *pay for performance* and/or *pay for proof* agreements with the marketing authorisation holder for esketamine in the fourth step. The *pay for performance* agreements can ensure that reimbursement only takes place when esketamine nasal spray has the desired effect.
A pay for proof agreement means that a lower price is reimbursed initially, but if more evidence is provided for the (cost) effectiveness of the treatment, a higher amount will be reimbursed.

Yours sincerely,

Peter Siebers
Acting Chair of the Executive Board