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2020030836

Our reference
2020030836

Date 17 August 2020
Subject Package advice ivacaftor/tezacaftor in combination with ivacaftor

Dear Ms van Ark,

In this letter, Zorginstituut Nederland informs you about tezacaftor/ivacaftor (Symkevi®) in combination with ivacaftor monopreparation (Kalydeco®) for the treatment of patients with cystic fibrosis.

The reason for this advice is your request, of 9 March 2020 (CIBG-20-0120), for a review to extend the further conditions of List 2 of the GVS (Medicines Reimbursement System) for the use of the combination preparation tezacaftor 100 mg/ivacaftor 150 mg (Symkevi®) in a combination schedule with ivacaftor 150 mg (Kalydeco®) monopreparation.

Zorginstituut Nederland has concluded that tezacaftor/ivacaftor in combination with ivacaftor monopreparation has a therapeutic added value compared to standard symptomatic treatment. However, there are uncertainties about the effects after 104 weeks. The costs of tezacaftor/ivacaftor in combination with ivacaftor monopreparation per patient are high, resulting in a high budget impact. In view of the above, the estimated cost-effectiveness is very unfavourable. Therefore, the Zorginstituut does not advise you to extend the further conditions set out in List 2 of the GVS unless a number of conditions are met by the occupational group on the one hand and the marketing authorisation holder on the other:

- A very substantial price reduction for tezacaftor/ivacaftor in combination with ivacaftor monopreparation, given the great uncertainty about the treatment effectiveness in terms of survival and quality of life, as well as the high budget impact and unfavourable cost-effectiveness.
- Appropriate use criteria for the efficient application of the treatment. The Zorginstituut is already in discussion with the occupational group about making arrangements for appropriate use.
- Tracking and recording long-term data by the occupational group to evaluate the effectiveness and safety of tezacaftor/ivacaftor in combination with ivacaftor monopreparation.
- The Zorginstituut advises you to enter into a European cooperation for (price) negotiations, to determine appropriate use and to evaluate medicinal products for the treatment of cystic fibrosis, also known as CFTR modulators.

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

Tezacaftor/ivacaftor (Symkevi®) and ivacaftor (Kalydeco®)
Symkevi® is a combination tablet. Each film-coated tablet contains 100 mg tezacaftor and 150 mg ivacaftor. Tezacaftor/ivacaftor (Symkevi®) is indicated in a combination schedule with ivacaftor (Kalydeco®) 150 mg tablets for the treatment of patients aged 12 years and older with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene or who are heterozygous for the F508del mutation and have one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

The current assessment is related to the second part of the above-mentioned indication for the treatment of tezacaftor/ivacaftor in combination with ivacaftor monotherapy. The first part of the above-mentioned indication is already included in the GVS as further conditions for List 2:

Line 121. Tezacaftor/Ivacaftor
only in combination with ivacaftor for the treatment of cystic fibrosis (CF) patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

Line 100. Ivacaftor
only for cystic fibrosis patients with the 'gating mutations' for which ivacaftor is registered,
or only in combination with tezacaftor/ivacaftor for the treatment of cystic fibrosis (CF) patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

General
At your request, the Zorginstituut assesses whether new care should be part of the insured package. The Zorginstituut bases its decision on the point of view of the basic insured package paid from joint premiums. We look at the degree of certainty that this will be achieved, both in the scientific sense and in public support, and we look at aspects of efficiency and transparency. The Zorginstituut is advised by two independent committees: the Scientific Advisory Council (WAR) for the scientific and practical assessment of the data and the determination of the cost-effectiveness, and the Package Advisory Committee (ACP) for the social assessment. We also consulted interested parties during the assessment process.

The Zorginstituut has assessed tezacaftor/ivacaftor in combination with ivacaftor monopreparation on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility.

Integral package criteria weighting
Irreversible damage to the lungs is the main cause of death in patients with cystic fibrosis. In this context, loss of lung capacity with age is the main determinant for

[1] Real-world package management 3 (2013). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

[2] Current state of science and practice assessment: updated version (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

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

the prognosis. As a result, the primary treatment goal in patients with cystic fibrosis is to maintain or improve lung function and reduce inflammation-induced lung damage. Currently, there is no treatment available that addresses the cause of the disease. These patients receive symptomatic treatment that has greatly improved survival and quality of life over the years.
Treatment with tezacaftor/ivacaftor in combination with ivacaftor monopreparation results in a clinically relevant improvement in lung function (ppFEV1), compared to standard symptomatic treatment. It is possible that tezacaftor/ivacaftor in combination with ivacaftor monopreparation reduces the number of pulmonary exacerbations. The beneficial effects of this combination treatment were demonstrated as a clinically relevant reduction of respiratory symptoms in cystic fibrosis patients with heterozygous F508del mutation and one of the above-mentioned mutations in the CFTR gene. Tezacaftor/ivacaftor in combination with ivacaftor monopreparation has a favourable safety profile, is well tolerated by patients and in the clinical study there were few patients who stopped using it due to its side effects. The Zorginstituut estimates that over a lifetime horizon the beneficial and adverse effects translate into an estimated incremental health gain of 5.6 QALY per patient, compared to standard symptomatic treatment.

However, the therapeutic added value of the combination treatment mentioned above, compared to standard symptomatic treatment, has only been demonstrated for a treatment period of 104 weeks: there is no data available on the safety and effectiveness after a treatment period of 104 weeks.

The annual treatment costs are €184,997 per patient. A total of 131 patients are expected to be eligible for the treatment with tezacaftor/ivacaftor in combination with ivacaftor monopreparation. Taking into account the risk of off-label use, the estimated number of patients is increased by 22. Extension of the further conditions of List 2 of tezacaftor/ivacaftor in combination with ivacaftor monopreparation for the above indication will be accompanied by additional costs charged to the pharmaceutical budget estimated at€24.2 to €28.3 million in year 3.

The Zorginstituut does not have sufficient confidence in the cost-effectiveness analysis carried out by the marketing authorisation holder. However, the results of the cost-effectiveness analysis are sufficient for decision-making.
There is in fact a great degree of certainty that with an ICER of at least €376,060 per QALY, the chance is 0% that tezacaftor/ivacaftor in combination with ivacaftor monopreparation is cost-effective at a reference value of €80,000 per QALY. The ICER depends on the amount of incremental costs compared to the level of health gain. The average incremental costs per patient over a lifetime horizon are estimated at €2,108,151 and are largely driven by the costs of the medicinal products tezacaftor/ivacaftor in combination with ivacaftor monopreparation.

In case of an ICER of at least €376,060 per QALY, the price of tezacaftor/ivacaftor in combination with ivacaftor monopreparation should decrease by at least 80% to fall below the upper limit of €80,000 per QALY.

Final conclusion
Looking at the uncertainties about the long-term effects of tezacaftor/ivacaftor in combination with ivacaftor monopreparation, the budget impact and cost-

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effectiveness, the Zorginstituut does not advise you to extend the further conditions set out in List 2 of the GVS unless the following conditions are met by the occupational group on the one hand and the marketing authorisation holder on the other:

- A very substantial price reduction for tezacaftor/ivacaftor in combination with ivacaftor monopreparation, given the great uncertainty about the treatment effectiveness in terms of survival and quality of life, as well as the high budget impact and unfavourable cost-effectiveness.
- Appropriate use criteria for the efficient application of the treatment. The Zorginstituut is already in discussion with the occupational group about making arrangements for appropriate use.
- Tracking and recording long-term data by the occupational group to evaluate the effectiveness and safety of tezacaftor/ivacaftor in combination with ivacaftor monopreparation.
- The Zorginstituut advises you to enter into a European cooperation for (price) negotiations, to determine appropriate use and to evaluate medicinal products for the treatment of cystic fibrosis, also known as CFTR modulators.

If the application of Symkevi® in combination with Kalydeco® is included in the package after a successful price negotiation, we recommend the following expansion of the reimbursement conditions:

Condition for tezacaftor/ivacaftor combination preparation (Symkevi®)
Only in combination with ivacaftor (Kalydeco®) for the treatment of cystic fibrosis (CF) patients aged 12 years and older who are heterozygous for the F508del mutation in the CFTR gene and have one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G or 3849+10kbC→T

Condition for ivacaftor (Kalydeco®)
Only in combination with tezacaftor/ivacaftor (Symkevi®) for the treatment of cystic fibrosis (CF) patients aged 12 years and older who are heterozygous for the F508del mutation and have one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G or 3849+10kbC→T

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board