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To the State Secretary of
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2021049960

Our reference
2021049960

Date 21 December 2021
Subject Tezacaftor/ivacaftor (Symkevi®) in combination with ivacaftor (Kalydeco®) extension of further conditions for use in patients with cystic fibrosis (CF) aged 6 to 11

Dear Mr Blokhuis,

This is a corrected version of the previously sent letter report dated 15 November 2021 (reference 202102867) in which the size of the additional costs has been corrected.

In your letter of 17 August 2021 (CIBG-21-2262), you asked the National Health Care Institute to carry out a review to extend the further conditions for reimbursement of tezacaftor/ivacaftor (Symkevi®) and ivacaftor monopreparation (Kalydeco®). The application for the extension of the further conditions is related to patients aged 6 to 11 with cystic fibrosis who are homozygous for the F508del mutation or 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, 5945L, 5977F, R1070W, D1152H, 2789+5G–A, 3272-26A-1G and 3849+10kbC-, T.

We will reply to your request in the form of a letter report.

Current situation
Since 1 August 2019, tezacaftor/ivacaftor (Symkevi®) has been included in the medicine reimbursement system (GVS) on List 1B, subject to further reimbursement conditions.

The current further conditions for tezacaftor/ivacaftor are:
Only in combination with ivacaftor for the treatment of cystic fibrosis (CF) patients aged 12 and older who are:

1. homozygous for the F508del mutation in the CFTR gene or
2. 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, 5945L, 5977F, R1070W, D1152H, 2789+5G–A, 3272-26A-1G and 3849+10kbC-, T.

Since 1 June 2015, ivacaftor (Kalydeco®) has been included in the medicine reimbursement system (GVS) on List 1B, subject to further reimbursement

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conditions.

The current further conditions for ivacaftor are:

1. Only for cystic fibrosis (CF) patients with the 'gating mutations' for which ivacaftor is registered, or
2. Only in combination with tezacaftor/ivacaftor for the treatment of cystic fibrosis (CF) patients aged 12 and older who are
    a. homozygous for the F508del mutation in the CFTR gene or
    b. 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, 5945L, 5977F, R1070W, D1152H, 2789+5G–A, 3272-26A-1G and 3849+10kbC-, T.

Expansion of the indication for children aged 6 to 11
In September 2020, the European Medicines Agency (EMA) approved the extension of the existing indication of tezacaftor/ivacaftor in combination with ivacaftor for CF patients aged 6 to 11 who are homozygous for the F508del mutation in the CFTR gene or heterozygous for the F508del mutation, and who have one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A-G, 5945L, 5977F, R1070W, D1152H, 2789+5G–A, 3272-26A-1G and 3849+10kbC-, T.

Conclusion of substantive assessment (See appendix)
Tezacaftor/ivacaftor (Symkevi®) in combination with ivacaftor monopreparation (Kalydeco®) has a therapeutic value which is comparable with that of lumacaftor/ivacaftor (Orkambi®) for the treatment of patients aged 6 to 11 with cystic fibrosis with a homozygous F508del mutation in the CFTR gene.

Tezacaftor/ivacaftor (Symkevi®) in combination with ivacaftor monopreparation (Kalydeco®) has added therapeutic value in comparison with standard symptomatic treatment for cystic fibrosis patients aged 6 to 11 with a heterozygous F508del mutation and who have one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A-G, 5945L, 5977F, R1070W, D1152H, 2789+5G–A, 3272-26A-1G and 3849+10kbC-, T.

It is assumed that 72 patients with the above stated indications will be treated with tezacaftor/ivacaftor (Symkevi®) in combination with ivacaftor monopreparation (Kalydeco®). Assuming 100% market penetration for patients with an F508del mutation with one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A-G, 5945L, 5977F, R1070W, D1152H, 2789+5G–A, 3272-26A-1G and 3849+10kbC-, T, in a market penetration of 50% in patients with homozygous mutation in the CFTR gene and 88% patient compliance, the treatment costs will amount to €112,523 per patient per year. Extension of the further condition of tezacaftor/ivacaftor (Symkevi®) in combination with ivacaftor (Kalydeco®) in patients with cystic fibrosis aged 6 to 11 with a homozygous F508del mutation or a heterozygous F508del mutation and one of the above mutations in the CFTR gene is associated with additional costs of €1.3 million charged to the pharmacy budget.

National Health Care Institute advice
Tezacaftor/ivacaftor (Symkevi®) in combination with ivacaftor monopreparation (Kalydeco®) has already been included on list 1B with further conditions. Based

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on the new research results, we advise you to extend the List 2 conditions of tezacaftor/ivacaftor (Symkevi®) and ivacaftor monopreparation (Kalydeco®) for the use in cystic fibrosis patients aged 6 to 11 years who are homozygous for the F508del mutation or 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, 5945L, 5977F, R1070W, D1152H, 2789+5G–A, 3272-26A-1G and 3849+10KBC, T. This extension of the further conditions is associated with additional costs of €1.3 million.

Extension further condition for tezacaftor/ivacaftor
Only in combination with ivacaftor for the treatment of cystic fibrosis (CF) patients ***aged 6 and older*** *who are:*

1. *homozygous for the F508del mutation in the CFTR gene or*
2. *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, 5945L, 5977F, R1070W, D1152H, 2789+5G–A, 3272-26A-1G and 3849+10kbC-, T.*

Extension further condition for ivacaftor
Only in combination with tezacaftor/ivacaftor for the treatment of cystic fibrosis (CF) patients ***aged 6 and older*** *who are:*

1. *homozygous for the F508del mutation in the CFTR gene or*
2. *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, 5945L, 5977F, R1070W, D1152H, 2789+5G–A, 3272-26A-1G and 3849+10kbC-, T.*

Yours sincerely,

Tiana van Grinsven
Acting Chair of the Executive Board

Appendix: Assessment of the extension of the further conditions and the budget impact analysis