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To the Minister of Health,  
Welfare and Sport  
P.O. Box 20350  
2500 EC DEN HAAG

0530.2016055466

Date 13 May 2016  
Re GVS report 16/08 on lumacaftor/ivacaftor (Orkambi®)

Dear Minister Schippers,

In your letter dated 8 February 2016 (CIBG-16-1619) you asked Zorginstituut Nederland to perform an assessment to answer the question whether the medicine lumacaftor/ivacaftor (Orkambi®) can be replaced with a drug which is currently included in the GVS. If this is not the case, you asked for an assessment of the therapeutic value of this drug for the approved indication as well as a pharmacoeconomic analysis.

Zorginstituut Nederland has completed its assessment of lumacaftor/ivacaftor. During the assessment, Zorginstituut Nederland was advised by two committees: the Scientific Advisory Committee (WAR) for a scientific assessment, and the Insured Package Advisory Committee (ACP) for a societal appraisal. You will find the scientific considerations in the GVS report, the pharmacotherapeutic report, the pharmacoeconomic report and the budget impact analysis.

### **Background to the drug and the disorder**

Lumacaftor/ivacaftor received market authorisation for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. Lumacaftor/ivacaftor is added to existing treatment (best supportive care).

CF is an autosomal recessive genetic disorder that is caused by a mutation in the CFTR gene. This disrupts the chloride ion transport, resulting in thick mucus. CF causes, among other things, an increase in respiratory infections with irreversible damage to the lungs and digestive tract. In the Netherlands, the median life expectancy of patients with CF is approximately 40 years.

### **Summary of the findings**

#### *Assessment of mutual replaceability*

Based on the GVS criteria, lumacaftor/ivacaftor can not be replaced by another drug in the GVS.

In order to determine whether the drug is eligible for placing on list 1B of the Health Insurance Regulation (GVS), its therapeutic value has to be determined as well as its cost-effectiveness and its budget impact.

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### **Appendices**

1. GVS-report on lumacaftor/ivacaftor (Orkambi®) (16/08)
2. Pharmacotherapeutic report
3. Pharmacoeconomic report
4. Budget impact analysis

### *Therapeutic value/effectiveness*

The assessment resulted in a therapeutic added value of lumacaftor/ivacaftor compared to best supportive care for the treatment of CF in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene. This means that the drug fulfils the health care package criterion 'effectiveness'.

### *Cost-effectiveness*

Zorginstituut Nederland concludes that the cost-effectiveness analysis is of insufficient methodological quality.

The deterministic incremental cost-effectiveness ratio determined by the manufacturer is estimated at approximately €360,000 per QALY. However, the Zorginstituut expects, due to uncertainties surrounding the input data, that the actual cost-effectiveness for the Dutch situation will be considerably less favourable. Based on the analysis of the manufacturer, Zorginstituut Nederland concludes that the chance that lumacaftor/ivacaftor is a cost-effective treatment is 0% based on a reference value of €80,000 per QALY.

### *Necessity*

Cystic fibrosis is regarded as an incurable disease with a reduced life expectancy. The burden of the disorder is partly dependent on the patient's CFTR genotype. The expected annual costs of lumacaftor/ivacaftor are €170,000 and the treatment duration is life-long. Therefore, in view of the burden of the disorder and its high costs, the drug fulfils the health care package criterion 'care that needs to be insured'.

### *Budget impact /Feasibility*

Zorginstituut Nederland expects, based on the registered indication, that 498 patients will be eligible for treatment with lumacaftor/ivacaftor. Taking into account the number of patients that fulfil the indication of lumacaftor/ivacaftor, including lumacaftor/ivacaftor on list 1B of the GVS will lead to the addition of €84.4 million to the pharmacy budget. However, if all patients, also those younger than 12 years, are treated who are homozygous for the F508del mutation in the CFTR gene, the additional costs will amount to €125.5 million. For this reason, it is important to attach conditions to its reimbursement, namely only reimburse the drug for patients for whom its therapeutic added value has been established (list 2 of the GVS). In addition, a more favourable price would increase the feasibility of lumacaftor/ivacaftor.

### **Advice Zorginstituut Nederland**

Based on the criteria for mutual replaceability, lumacaftor/ivacaftor is not eligible for placement on GVS list 1A.

Lumacaftor/ivacaftor has a therapeutic added value, and thus fulfils the health care package criterion 'effectiveness'. The estimated additional costs to the pharmacy budget for this indication are considerable, namely between €84,4 and €125,5 million. This involves a high chance of implicit replacement of other more cost-effective care, leading to loss of health at population level.

Furthermore, the cost-effectiveness analysis is of insufficient quality. In the most favourable scenario, the chance that lumacaftor/ivacaftor is a cost-effective treatment is 0% based on a reference value of €80,000 per QALY.

Zorginstituut Nederland has reached the following conclusions:

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- We are unable to realistically estimate the cost-effectiveness and are unable to advise the Minister which price reduction is needed to get anywhere near to an acceptable cost-effectiveness.
- The majority of patients do not respond to treatment. It is important to exclude the non-responders before treatment (and reimbursement) is started. The diagnostic test which can be used to select these patients, however, has not yet been validated.
- We may be willing to accept a higher estimation of the incremental cost-effectiveness ratio than the reference value of €80,000 per QALY, when a more realistic estimation of the cost-effectiveness is available and the manufacturer is transparent about the way in which they determined the price of lumacaftor/ivacaftor.
- Reimbursement of lumacaftor/ivacaftor from the basic health care package would implicitly replace more cost-effective care. At population level, this will result in loss of health.

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Important factors that influenced Zorginstituut Nederland's decision were that the manufacturer did not provide a realistic estimate of the cost-effectiveness and for not being transparent on the price of the drug. Adding lumacaftor/ivacaftor to the health care package at its current price will unavoidably lead to replacement of other care because our health care budget is, in principle, limited. The addition will lead to a loss of health at a population level and makes a more accurate determination of cost-effectiveness necessary. It is primarily the responsibility of a manufacturer to provide this more precise estimate, and will enable Zorginstituut Nederland to formulate a well-informed advice and, if acceptable, accept a cost effectiveness value above €80,000 per QALY, and inform the minister on the price reduction that is required to realise this.

The Zorginstituut therefore feels that currently lumacaftor/ivacaftor is not eligible for placement on list 1B.

The Zorginstituut is aware of the consequences for the patients concerned and their families. The manufacturer of lumacaftor/ivacaftor is in a position to alter this. For instance, by supplying an accurate estimation of the cost-effectiveness. In addition, a validated diagnostic test can improve the drug's (cost-) effectiveness. Zorginstituut Nederland will re-assess the drug's cost-effectiveness, if the manufacturer is transparent on the price of lumacaftor/ivacaftor. After all, the drug's cost-effectiveness is largely determined by the price, and the value of the incremental cost-effectiveness ratio is many times higher than the reference value, more transparency is needed with regards to the factors that influenced the price of the drug.

If these preconditions are fulfilled, the Zorginstituut is prepared to re-assess the product.

Yours sincerely,

Arnold Moerkamp  
*Chairman of the Executive Board*

*The original text of this excerpt from a **WAR-Report** of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's WAR-Report.*

*Furthermore, Zorginstituut Nederland points out that only the letter to the minister of Health Welfare and Sport was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.*

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