Lumacaftor/ivacaftor (Orkambi®) for the treatment of cystic fibrosis

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 30 April 2019

Zorginstituut Nederland carried out a marginal assessment in relation to extending the specific conditions for the medicinal product lumacaftor/ivacaftor (Orkambi®), and concluded as follows.

In a letter dated 12 March 2019 (CIBG-19-07833), the Minister of Health, Welfare and Sport asked *Zorginstituut Nederland*, in response to an extension in the indication of lumacaftor/ivacaftor (Orkambi®), to alter its specific condition to 'only for cystic fibrosis (CF) patients aged **2** years and older who are homozygous for the *F508del* mutation in the CFTR gene'. The manufacturer subsequently asked for placement on List 1B of the Medicines Reimbursement System (GVS) of a new pharmaceutical form in two strengths that was developed for patients aged *2 to 5* years.

As the Minister's request relates to an alteration in an existing indication for lumacaftor/ivacaftor, we will reply to the request to extend the specific conditions in the form of a letter. Our answer is based on new research results (study 115).

Current situation
Since November 2017 lumacaftor/ivacaftor (Orkambi®) film-coated tablets have been included on List 1B and List 2 of the GVS for use in CF patients aged *12* years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. As of 1 May 2018, the specific condition was extended to include use in patients aged *6 to 11* years. The current condition reads: "*Only for cystic fibrosis (CF) patients aged 6 years and older who are homozygous for the* F508del *mutation in the CFTR gene".*

Newly registered indication for lumacaftor/ivacaftor (Orkambi®)
In January 2019, based on new research data, the European Medicines Agency (EMA) approved extension of the existing Orkambi® indication with use in CF patients aged *2 to 5* years who are homozygous for the *F508del* mutation in the *CFTR* gene. The permit-holder is also asking for a new pharmaceutical form in two strengths to be placed on List 1B: 100 mg/125 mg sachet of lumacaftor/ivacaftor (Orkambi®) granules and 150 mg/188 mg sachet of granules, both for oral administration, which were developed for this younger category of patients.

Dosage
The recommended daily dose for patients aged *2 to 5* years and weighing *less than 14 kg* is one sachet 100 mg lumacaftor/125 mg ivacaftor granules orally every 12 hours. This amounts to a total daily dose of 200 mg lumacaftor/250 mg ivacaftor.
The recommended daily dose for patients aged *2 to 5* years and weighing *14 kg or more* is one sachet of 150 mg lumacaftor/188 mg ivacaftor granules orally every 12 hours. This amounts to a total daily dose of 300 mg lumacaftor/376 mg ivacaftor.

Assessment conclusion
Evidence for the efficacy of lumacaftor/ivacaftor in CF patients aged 2 to 5 years who are homozygous for the *F508del* mutation is very scarce. Nevertheless, based on indirect evidence (sweat-chloride concentration), and evidence among older children and adults, we advise extending the List 2 conditions to include use in patients aged 2 to 5 years.

If we assume that all 73 children will be treated with lumacaftor/ivacaftor, 100% market penetration and 100% therapy compliance, extending the specific condition of lumacaftor/ivacaftor with cystic fibrosis patients aged 2 to 5 years with a homozygous *F508del mutation* in the *CFTR* gene will be accompanied by total additional costs of **€11 million** to the pharmacy budget.

Advice of *Zorginstituut Nederland*
Lumacaftor/ivacaftor (Orkambi®) has already been placed on List 1B with a specific condition. Based on the new study results (study 115) and the budget impact analysis, we advise the Minister to extend the List 2 conditions of Orkambi® to include use in patients aged *2 to 5* years. Orkambi® 100 mg/125 mg sachet of granules and 150 mg/188 mg sachet of granules can be added to list 1B. This extension in the specific condition will be accompanied by additional costs amounting to €11 million.

Extension in the specific condition of lumacaftor/ivacaftor:
"*Only for cystic fibrosis (CF) patients aged 2 years and older who are homozygous for the F508del mutation in the CFTR gene".*

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The original text of this excerpt from advice 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 advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.