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Combination of cystic fibrosis medicines to treat patients with rare mutations

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Positive opinion for extension of indication brings disease-modifying treatment to all cystic fibrosis patients with modulator responsive mutations

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EMA's human medicines committee (CHMP) has recommended extending the therapeutic indication of two medicines, Kaftrio (ivacaftor / tezacaftor / elexacaftor) and Kalydeco (ivacaftor) for the treatment of cystic fibrosis, to include their use in combination for patients aged two years and older who have at least one non-class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Cystic fibrosis is an inherited disease that has severe effects on the lungs, the digestive system and other organs. It comes with high premature mortality. Cystic fibrosis can be caused by various mutations in the gene for a protein called the 'cystic fibrosis transmembrane conductance regulator'. The CFTR protein regulates the production of mucus in the lungs and digestive juices in the gut. Some mutations affect the way the protein works, resulting in mucus and digestive fluids being too thick, which leads to blockages,

inflammation, increased risk of lung infections, and poor digestion and growth. Other mutations, called class I mutations, result in no CFTR protein being produced.

Kaftrio and Kalydeco are used in combination to treat patients whose cystic fibrosis is due to at least one mutation in the CFTR gene that causes abnormal or insufficient CFTR protein production. The medicines work together to improve the function of these abnormal CFTR proteins, thereby targeting the underlying cause of the disease. Their actions combine to make lung mucus and digestive juices less thick, thus helping to relieve symptoms of the disease.

While medicines like Kaftrio and Kalydeco, also called CFTR modulators (i.e. correctors and potentiators), have dramatically improved outcomes for some patients, they don't work for all mutations. Certain patients still face severe disease progression despite treatment. The extension of indication will allow all patients likely to respond to these modulator therapies to be treated, meaning that around 95-97% of cystic fibrosis patients in the European Union (EU) could benefit from these therapies. This represents an additional 15-17% of patients who could be treated compared with the current indication. The remaining patients do not respond to modulator therapies (patients with two class I mutations that do not produce the CFTR protein).

The CHMP based its recommendation on the assessment of efficacy and safety data from clinical and in vitro (laboratory) studies, including one randomised placebo-controlled trial, an open-label study, data from a real-world evidence study conducted by the United States Cystic Fibrosis Foundation as well as bibliographical data obtained through a French compassionate use programme.

The safety profile of this combination of medicines was generally consistent with previous observations. The most common side effects are headache, diarrhoea, upper respiratory tract infection and increased liver enzymes. Serious rashes were reported in very rare cases.

The opinion adopted by the CHMP is an intermediary step on Kaftrio and Kalydeco's path to patient access. The opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide extension of the

therapeutic indication. Once an extension has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role or use of these medicines in the context of the national health system of that country.

Notes:

1. The marketing authorisation holder for Kaftrio and Kalydeco is Vertex Pharmaceuticals (Ireland) Limited.
2. Kaftrio received an orphan designation on 14 December 2018.
3. Literature reference: The relative frequency of CFTR mutation classes in European patients with cystic fibrosis.

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