Advice for clinicians on Cataract Related to CFTER Modifying Drug of Cystic Fibrosis

Several drugs which modify the cystic fibrosis conductance regulator gene (CTFR), manufactured by Vertex pharmaceuticals, are indicated for the treatment of cystic fibrosis (CF). These drugs include Orkambi®, Kalydeco® and Symkevi®. All three of these drug treatments contain the drug Ivacaftor, either as monotherapy or in combination with other drugs. These increase the number of functional chloride channels expressed on the cell surface with a resultant improvement in pulmonary function and reduced pulmonary exacerbations.

Recently, the CFTR modifier, Orkambi (Ivacaftor/Lumacaftor), indicated in children from 2 years of age with CF homozygous for the Phe508del CTFR mutation, received approval from NHS England who agreed to a “managed access” scheme for 2 years with the manufacturer. The Scottish Government has agreed to a 5-year interim programme with the manufacturer to grant access to patients for treatment with these drugs. It is estimated that over 4000 patients may be eligible for the treatment. A condition of these agreements is that a full portfolio and data should be collected and submitted to NICE and The Scottish Medicines Consortium respectively.

Non-congenital cataracts were noted in preclinical studies in juvenile rats, at all dose levels, and in children and adolescents taking Ivacaftor and combination Lumicaftor/Ivacaftor (Guevera MT, McColley SA. The safety of lumacaftor and ivacaftor for the treatment of cystic fibrosis. Expert Opin Drug Saf. 2017; 16(11):1305–1311.). Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to Ivacaftor could not, in their view, be excluded. The manufacturers therefore recommend baseline and periodic eye examinations.

Vertex has included this recommendation within their patient information leaflet for children or adolescent patients, stating that their “doctor should perform eye examinations before and during treatment with Orkambi to look for cataracts”. This recommendation is also made for other drug combinations which contain Ivacaftor.

Vertex have provided evidence from clinical trials of Orkambi and other trials involving the use of Ivacaftor in relation to cataract. From review of the data provided it is our view that the risk of cataract development remains poorly defined and causality related to drug is unclear as cataracts were also observed in those within the trials receiving placebo. Furthermore, the cataracts were not considered to be visually significant in most cases. In the case of Orkambi, no cataract was observed in the age range of 2-5-year olds.

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Advice for Clinicians
The Royal College of Ophthalmologists is willing to review any further clinical and methodological data, and any future real-world results, from Vertex. At this time, based on the data received, there is no evidence to support a recommendation for wholesale adoption of a hospital eye service screening programme for cataracts in children who are prescribed CFTR modifiers containing Ivacaftor.

We do not believe that this should stop clinicians prescribing CFTR modifying agents where it is clinically appropriate, but parents of young children should be informed of the uncertain risk of development of cataracts when considering commencement of treatment. The College, however, does not endorse the routine referral of such patients to ophthalmology for cataract screening unless there is clinical suspicion of visual difficulties.

Clinicians starting children on treatment with CFTR modifying agents should recommend children are seen on a regular basis by their local optometrist. We believe that this should be enough in most cases to detect any significant visual difficulties which may prompt referral to hospital eye services for further assessment.

Paediatric Subcommittee
The Royal College of Ophthalmologists
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