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Clinical Expert Summary
Ivacaftor (Kalydeco®) 150 mg film-coated tablets

Ivacaftor (Kalydeco®) for the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an *R117H* mutation in the CF transmembrane conductance regulator (*CFTR*) gene.

1. Existing guidelines

Clinical experts highlight the Welsh Specialised Services Committee (WHSSC) Specialised Services Policy Document CP46: Ivacaftor (Kalydeco®) for Cystic Fibrosis (CF) (*G551D* and other specific Non-*G551D* mutations). This document is undergoing expansion to include children aged 2–5 years weighing < 25 kg but this policy does not currently cover the *R117H* mutation (Arg117His-*CFTR* mutation).

2. Disease prevalence/incidence

There are 13 adult patients in Wales who are known to carry *R117H* mutation. Seven patients have the mutation *R117H*/5T, four patients have the mutation *R117H*/7T and there are two patients who have the *R117H* mutation but it is not known if they are 5T/7T. Of the 13 adult patients there would be 6 patients eligible for treatment.

An expert highlighted that *R117H* is not one of the eight *CFTR* mutations screened at birth in Wales, therefore patients will be detected through newborn screening only if they are heterozygous for one of the eight most common mutations currently screened, and would progress to a sweat test, (only those with a sweat test > 30 mmol/l would then be tested for *R117H*). Testing for the thymine repeats are part of the routine 50 mutation screening done in older patients.

3. Current treatment options

The standard CF treatment as per UK CF trust standards of care was highlighted.

4. Unmet needs

Clinical experts noted that *R117H* mutation causes impaired *CFTR* channel conductance and reduced channel gating. In affecting the basic gene defect ivacaftor has the potential to transform the disease process to CF and such therapies are best used in early disease rather than later when deterioration becomes self-perpetuating irrespective of therapy. Experts highlight there is evidence to suggest that patients with the *R117H* mutation become symptomatic at an older age but then decline at the same rate as patients with more severe mutations. Clinical experts highlighted there is an unmet need for these patients.

Clinical experts across Wales provided a consensus statement and were in agreement as to which patients with *R117H* should receive ivacaftor. A proposed algorithm has been developed so that ivacaftor treatment for patients with *R117H* mutation is targeted to those individuals in which it will offer a significant benefit. Clinicians expressed their strong support for ivacaftor to be available for patients with *R117H* according to this algorithm.

5. Knowledge of product in given indication

It was highlighted that *R117H* mutation results in both impaired *CFTR* channel gating and conductance. As the gating impairment is the more profound, ivacaftor should be an attractive therapy. *R117H* is associated with marked phenotypic variability dependent on the length of the intron 8 poly-thymidine (poly-T) tract. The 7T poly-T variant is associated with greater *CFTR* production than the 5T variant, and does not seem to be associated with significant lung disease in childhood.

Clinical experts reported that the use of ivacaftor in *R117H* would be targeted to those most likely to benefit from ivacaftor and there is a consensus from all prescribers in Wales on the criteria that patients with the *R117H* mutation will have to fulfil if they are to receive ivacaftor. A proposed algorithm for use of ivacaftor has been agreed by all clinicians in Wales. The criteria listed in the proposed algorithm are: age ≥18 years, presence of a 2nd recognised CFTR disease-causing allele, and presence of end-organ damage with CT evidence of significant bronchiectasis. The algorithm for treatment states that patient compliance should be demonstrated and standard CF therapy optimised. There would also have to be a consensus between respective consultant physicians in order to prescribe ivacaftor.

It should be noted that one expert involved in compiling this response declared a non-personal, non-specific interest in relation to ivacaftor for the indication under consideration.