AWMSG Secretariat Assessment Report – Limited submission
Ivacaftor (Kalydeco®▼) 50 mg and 75 mg granules

Company: Vertex Pharmaceuticals (Europe) Ltd

Licensed indication under consideration: Ivacaftor (Kalydeco®▼) granules are indicated for the treatment of children with cystic fibrosis (CF) aged two years to less than six years and weighing less than 25 kg who have one of the following gating (class III) mutations in the CF transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Date of licence extension: 16 November 2015

Comparator(s)

The comparator included in the company submission was standard of care treatments.

Limited submission details

The limited submission criteria were met based on a minor licence extension.

Clinical effectiveness

- Ivacaftor (Kalydeco®) was previously licensed and recommended for use in NHS Wales in patients aged six years and older with one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R; this submission covers the licence extension for the granules formulation and the extension for use in children aged two to less than six years, weighing less than 25 kg.
- Ivacaftor is the first and only licensed CFTR potentiator that treats the underlying cause of disease and addresses an unmet need for children aged 2 to < 6 years.
- The submission included a two-part, phase III, open-label, single-arm study (KIWI) investigating the safety, pharmacokinetics, pharmacodynamics and efficacy of ivacaftor in patients aged two to five years with cystic fibrosis and a CFTR gating mutation, recruited from 15 hospitals in the USA, UK and Canada.
- Participants received oral ivacaftor 50 mg (bodyweight < 14 kg) or 75 mg (bodyweight ≥ 14 kg) every 12 hours for four days in part A (n = 9), and then for 24 weeks in part B (n = 34). In part A all participants had a G551D-CFTR mutation and in part B 32 (94%) had a G551D mutation and two (6%) had S549N mutation.
- Results of ivacaftor pharmacokinetics suggested that exposure was similar to that reported in adults. Ivacaftor statistically significantly ($p < 0.0001$) decreased sweat chloride concentration, which is a direct measure of CFTR activity, as early as week two, with such effects sustained through to week 24. The mean absolute change from baseline to week 24 was −46.9 mmol/L.
- No new adverse events were identified in the KIWI study and therefore the

Committee for Medicinal Products for Human Use (CHMP) concluded that the safety profile of ivacaftor in children aged two to five years with a CFTR gating mutation was consistent with those observed in previous studies recruiting older children and adolescents. However, there is a concern that in young children hepatocellular injury occurs more frequently and is of a higher magnitude as compared to older age groups. CHMP concluded that liver toxicity can be managed through appropriate monitoring in clinical practice.

- A long-term extension study (KLIMB), requested by CHMP post-authorisation, addressing the efficacy and safety of ivacaftor in this age range is ongoing. The expected publication date of results is 2017.

Budget impact

- The company has reported that based on clinical expert opinion there would be one patient with G551D CFTR mutation eligible for this medicine in Wales. The company has estimated there will be less than one incident case per year. Clinical expert opinion sought by the All Wales Therapeutics and Toxicology Centre (AWTTC) concurred with the company estimates for prevalence and advised there is one patient eligible for treatment and within the next two years there would be two further patients eligible for treatment with ivacaftor with an estimated incidence of one new eligible patients every two and a half years.
- Based on a Wales Patient Access Scheme (WPAS) discount price and there being one eligible patient in year one, the company estimate the budget impact is [commercial in confidence figure removed] in year one rising to [commercial in confidence figure removed] in year five based on there being four patients.
- As is the case for all high cost medicines, a small variation in eligible patient numbers can have a significant impact on budget impact.

Consideration of All Wales Medicines Strategy Group (AWMSG) policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases.

- Ivacaftor has been granted orphan status by the EMA. The prevalence of CF is estimated to be 1.2 in 10,000 people. Gating mutations are reported to be present in approximately 3% of the CF patient population worldwide and in the EU. The UK CF registry data reports there are an estimated 434 CF patients treated in Wales. The total number of patients eligible for treatment with ivacaftor is 29. Of these 29, 13 are G551D; three are non-G551D and 13 patients with the R117H gating mutation. AWTTC consider ivacaftor eligible to be appraised as an ultra-orphan medicine as the full population of the licensed indication does not exceed the threshold of ≤ 1 in 50,000 in the UK (or ≤ 60 patients in Wales). The New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 1) if they consider ivacaftor as an ultra-orphan medicine and the cost per QALY is above the normal thresholds applied.

Table 1. Evidence considered by NMG/AWMSG.

NMG/AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	CF is a life-limiting condition; the leading cause of mortality is progressive loss of lung function. Current therapies alleviate symptoms only and require time and effort that imposes a significant burden on patients' and their carers' quality of life.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	Standard care can be considered as daily prophylactic medications and supplements such as pancreatic enzymes, nutritional and vitamin supplements, oral or nebulised antibiotics, nebulised mucolytic agents and daily physiotherapy, hence there is an unmet need for an effective therapy that targets the underlying cause of CF.
Whether the medicine can reverse or cure, rather than stabilise the condition	There is no evidence that ivacaftor can reverse or cure the condition. Short-term treatment with ivacaftor for patients with non-*G551D* mutations has shown clinically relevant improvements in pulmonary function, pulmonary exacerbations, BMI, CFQ-R respiratory domain scores and *CFTR* function (as measured by sweat chloride concentration).
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development	The company highlight that gene therapy is currently being explored through clinical trials. Ivacaftor does not bridge a gap to gene therapy.
The innovative nature of the medicine	Ivacaftor belongs to a new class of medicines called the *CFTR* modulators, which target the pathophysiology of CF by restoring the function of the *CFTR* protein. Current CF treatments are aimed at alleviating symptoms of the condition.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	The disease has a negative impact on the ability of patients to work and may result in time off work or education. The company highlight the physical and psychological impact of the disease and that treatment burden is substantial. The company report that ivacaftor has shown clinically relevant improvements in pulmonary function which will allow patients to remain in education or work for a longer period of time.
Added value to the patient's family (e.g. impact on a carer or family life)	Mental health problems including anxiety and depression are reported in carers for patients with CF. The company report that the amount of time spent caring for patients with CF has a negative impact on daily activities, family life, social activities and work productivity and the company suggest that the clinical benefits of ivacaftor will translate to an improvement in the general health of carers of patients with cystic fibrosis.

Additional information

- AWTTC is of the opinion that, if recommended, ivacaftor (Kalydeco®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.
- The company anticipate that ivacaftor (Kalydeco®) may be supplied by a home healthcare provider.

Evidence search

Date of evidence search: 3 August 2016.
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Ivacaftor (Kalydeco®) 50 mg and 75 mg granules. Reference number: 2770. December 2016.