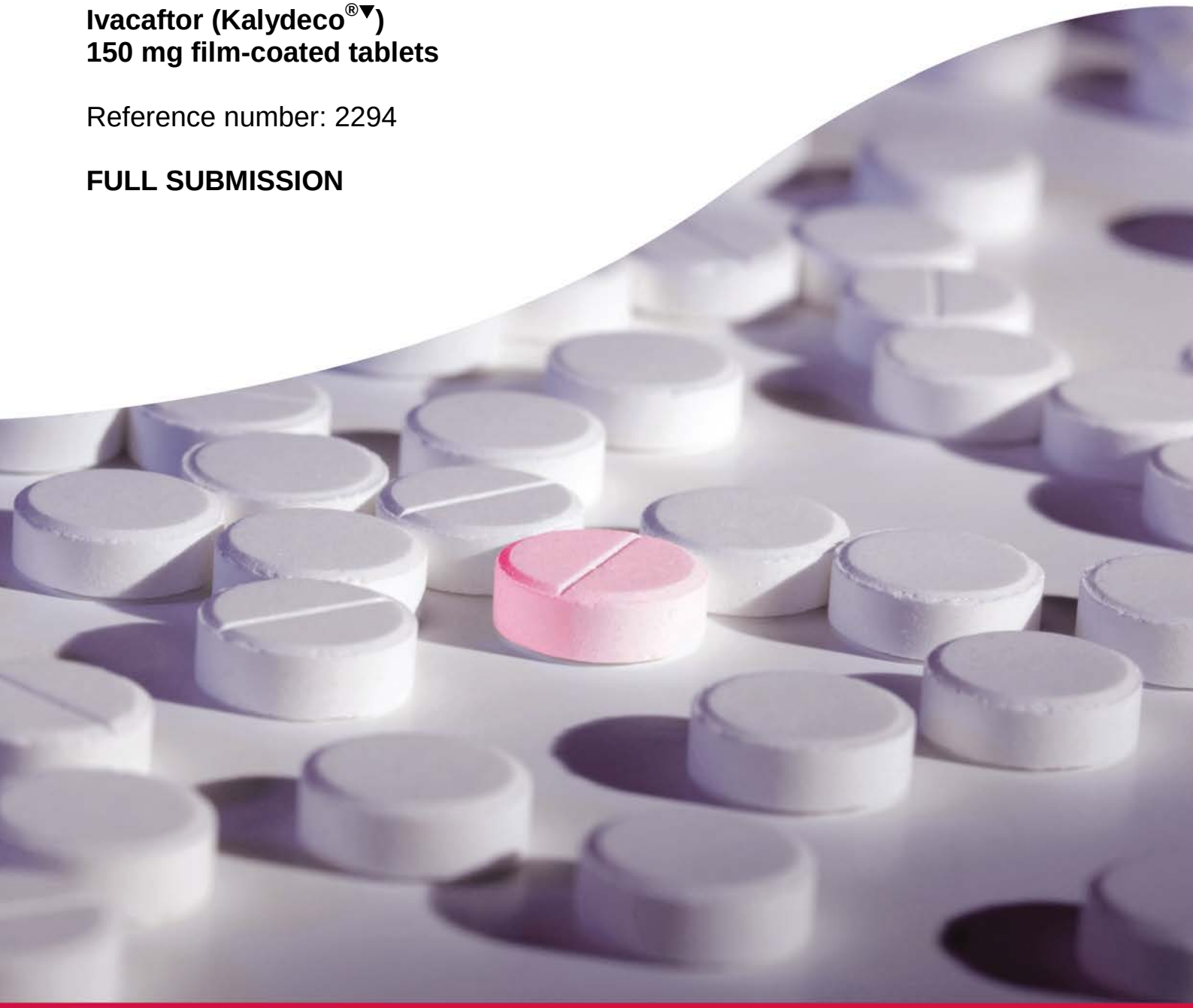
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Ivacaftor (Kalydeco®▼)
150 mg film-coated tablets

Reference number: 2294

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Ivacaftor (Kalydeco®▼) 150 mg film-coated tablets

This assessment report is based on evidence submitted by Vertex Pharmaceuticals (UK) Ltd on 27 April 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Ivacaftor (Kalydeco®▼) for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following gating (class III) mutations in the CF transmembrane conductance regulator (*CFTR)* gene: *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R.* Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2].
Dosing	The recommended dose is 150 mg taken orally every 12 hours[2].
Marketing authorisation date	28 July 2014[3] (licensed for the treatment of cystic fibrosis in patients aged six years and older who have a *G551D* mutation in the *CFTR* gene on 23 July 2012).

2.0 DECISION CONTEXT

2.1 Background

Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting approximately 1 in 2,500 live births[4]. The condition is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, which encodes a chloride channel that is essential for the regulation of salt and water movements across cell membranes[4]. Although CF affects multiple organs, including the lungs, digestive system and vas deferens[4], the leading cause of mortality is the progressive loss of lung function[5]. The airways become clogged with thick sticky mucus which impairs the clearance of microorganisms, leading to recurrent infection, inflammation, bronchial damage, bronchiectasis and eventually death from respiratory failure[4]. Current CF treatments aim to alleviate symptoms of the condition, and include infection control, respiratory and nutritional care[4].

More than 1,500 *CFTR* mutations that cause CF have been identified, but the functional importance is known only for a small number[5]. Ten *CFTR* mutations that lead to a *CFTR* gating functional defect have been identified: *G551D, G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P,* and *G1349D*. Gating refers to the amount of time in which the *CFTR* channel is open and can transport chloride, and a gating mutation results in a *CFTR* protein with a primary defect of low channel open probability compared to normal *CFTR*. Gating mutations are present in approximately 5% of the CF patient population worldwide and in the EU. Approximately 4% of patients have the *G551D* mutation (approximately 1083 patients in the EU and 2374 worldwide), and the remaining 1% has other gating mutations (205 subjects in the EU and 370 worldwide)[5]. There are few published reports on the clinical features of patients with other non-*G551D* mutations; however an analysis of the USA CF Foundation Patient Registry data revealed that the rates of lung disease progression in patients with these mutations are similar to that of patients with the *G551D* mutation[5].

Ivacaftor (Kalydeco®▼) 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[5]. Ivacaftor is a type of *CFTR* modulator known as a *CFTR* potentiator,

which acts on the *CFTR* protein to increase the gating to enhance chloride transport[5]. In 2012, ivacaftor was authorised by the European Medicines Agency (EMA) for the treatment of CF in patients aged six years and older who have a *G551D* mutation in the *CFTR* gene[6] and has been made available in Wales for eligible patients with this mutation[7]. The current submission presents data supporting the licensed extension of ivacaftor covering eight additional (non-*G551D*) gating mutations: *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* and *S549R*[5].

2.2 Comparators

The comparator included in the company submission was best supportive care (BSC).

2.3 Guidance and related advice

- Welsh Health Specialised Services Committee (WHSSC). Specialised services clinical access policy: ivacaftor (Kalydeco) for *G551D* cystic fibrosis (2014)[8].
- Cystic Fibrosis Trust. Standards for the clinical care of children and adults with cystic fibrosis in the UK (2011)[4].
- Kerem E, Conway S, Elborn S, et al. Standards of care for patients with cystic fibrosis: a European consensus (2005)[9].

The AWMSG has previously issued a recommendation for the use of ivacaftor (Kalydeco®▼). Subsequent to AWMSG recommendation, this medicine has been made available in Wales[7].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of one phase III study, KONNECTION, conducted to evaluate the efficacy and safety of ivacaftor in patients with CF and with a non-*G551D-CFTR* gating mutation[1,10].

3.1 KONNECTION study

KONNECTION was a multicentre, international, two-part, randomised, placebo-controlled, crossover study with an open-label period[1,5,10]. In Part 1, 39 patients were randomised 1:1 to one of two treatment sequences. Treatment sequence 1 consisted of ivacaftor 150 mg twice a day for eight weeks followed by a four- to eight-week washout period and then placebo for eight weeks; treatment sequence 2 consisted of placebo for eight weeks followed by a four- to eight-week washout period and then ivacaftor 150 mg twice a day for eight weeks. Immediately after the end of Part 1, patients moved into a 16-week open-label period of ivacaftor treatment (Part 2 of the study). Patients were followed up four weeks (± seven days) after the last dose[1,5,10].

Patients were ≥ six years of age, had at least one of nine non-*G551D-CFTR* gating mutations (i.e. *G970R, G178R, G551S, S549N, S549R, G1244E, S1251N, S1255P* or *G1349D*) and had a FEV_1 of ≥ 40% of predicted at screening[1,5,10]. At least two patients with each of the genotypes were enrolled[1,5,10]. Patients were stratified for age and FEV_1 severity, and the majority of patients were white (74.4%)[5].

In Part 1, the primary endpoint was the absolute change from baseline in percent of predicted forced expiratory volume in one second (FEV_1: see Glossary) through eight weeks of blinded treatment[1,5,10]. Absolute mean change from baseline in percent predicted FEV_1 through 24 weeks of treatment was the primary endpoint for Part 2. Secondary endpoints included safety, change in nutritional status (Body Mass Index [BMI]), change in *CFTR* function (sweat chloride concentration) and respiratory symptoms (CF Questionnaire Revised [CFQ-R]: see Glossary). Tertiary endpoints included pulmonary exacerbations (see Section 3.2) as a measure of safety[1,5,10].

Using mixed-effects model for repeated measures (MMRM), the mean absolute change from baseline in percent predicted FEV_1 through week eight was significantly greater during ivacaftor treatment (7.49%) than during placebo (−3.19%): the treatment difference was 10.68% (95% confidence interval [CI]: 7.26 to 14.10; $p < 0.0001$)[1,5,10]. See Table 1 for results. This effect was consistent throughout the open-label Part 2 of the study: the change from baseline through 16 weeks of ivacaftor was 10.44% (patients receiving treatment sequence 1), and through 24 weeks of ivacaftor was 13.53% (patients receiving treatment sequence 2)[1]. See Table 2 for results. These figures were supported by statistically significant results for secondary endpoints through eight weeks (BMI, sweat chloride and CFQ-R: see Table 1), and were consistent throughout the open-label Part 2 of the study[1] (see Table 2).

Table 1. Results of efficacy endpoints through 8 weeks of treatment.

Endpoint	Ivacaftor LS mean (n = 38)	Placebo LS mean (n = 37)	Treatment difference	P-value* (95% CI)
Absolute change from baseline in percent of predicted FEV_1 (%)†	7.49	−3.19	10.68	< 0.0001 (7.26 to 14.10)
Absolute change from baseline in BMI (kg/m^2)§¶	0.68	0.02	0.66	< 0.0001 (0.34 to 0.99)
Absolute change from baseline in BMI-for-age *z*-score (kg/m^2)§¶	0.24	−0.04	0.28	0.0010 (0.12 to 0.45)
Absolute change from baseline in sweat chloride (mmol/l)¶	−52.28	−3.11	−49.17	< 0.0001 (−56.95 to −41.38)
Absolute change from baseline in pooled CFQ-R respiratory domain score (points)¶**	8.94	−0.67	9.61	0.0004 (4.49 to 14.73)

* P values are unadjusted for multiple comparisons.
† Primary endpoint.
§ Treatment effect was evaluated by rate of change per 56 days. See Glossary for definition of z score.
¶ Secondary endpoint.
** Pooled was defined as all questionnaire versions except for the parent/caregiver version.

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire Revised (see Glossary); CI: confidence interval; FEV_1: forced expiratory volume in one second (see Glossary); LS: least squares.

Table 2. Results of efficacy endpoints from 16 and 24 weeks of ivacaftor treatment.

Endpoint	16 weeks of ivacaftor Part 1, treatment sequence 1 (ivacaftor – placebo) n = 18	24 weeks of ivacaftor Part 1, treatment sequence 2 (placebo – ivacaftor) n = 18
Absolute change from baseline in percent of predicted FEV_1 (%)*	10.44 (13.25)	13.53 (10.18)
Absolute change from baseline in BMI (kg/m^2) †§	0.44 (1.10)	1.26 (0.76)
Absolute change from baseline in sweat chloride (mmol/l) §	−43.03 (33.48)	−59.24 (32.57)
Absolute change from baseline in pooled CFQ-R respiratory domain score (points) §¶	9.10 (16.72)	11.42 (13.60)

* Primary endpoint.
† Treatment effect was evaluated by rate of change per 56 days.
§ Secondary endpoint.
¶ Pooled was defined as all questionnaire versions except for the parent/caregiver version.

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire Revised (see Glossary); FEV_1: forced expiratory volume in one second (see Glossary).

3.2 Safety

The safety profile of short-term (eight weeks) ivacaftor treatment in patients with non-*G551D* gating mutations included in the KONNECTION study was consistent with that observed in previous phase III studies (STRIVE[11] and ENVISION[12]) of patients with a *G551D* mutation[1,5,10]. The EMA concluded that no new safety concerns emerged from the KONNECTION study[5].

In the KONNECTION study, the proportion of patients with adverse events (AEs) was lower during ivacaftor treatment (73.7%) than during placebo (83.8%)[1,5,10]. The most common AE and serious AE (SAE) during both treatments was infective pulmonary exacerbation of CF: this occurred with a lower incidence during ivacaftor treatment than during placebo (23.7% and 29.7%, respectively). No patients had AEs that led to discontinuation and no deaths were reported during the study[1,5,10].

3.3 AWTTC critique

- The safety profile and positive treatment effects demonstrated in the KONNECTION study of patients with non-*G551D* mutations are consistent with the findings observed in previous phase III studies (STRIVE, ENVISION and PERSIST [an open-label extension study of STRIVE and ENVISION]) of patients with a *G551D* mutation.
- There is currently no licensed medicine available in Wales for patients with gating mutations in the *CFTR* gene which targets the underlying defect in CF, rather than alleviating symptoms[1].
- The EMA raised concerns regarding the heterogeneity of gating mutations and the patient population included in the KONNECTION study, as well as on whether all of the non-*G551D* gating mutations assessed in the study were disease-causing[5]. As a consequence, the indication was limited to the specific mutations that were assessed in the KONNECTION study, excluding patients carrying the *G970R* gating mutation as for this mutation efficacy could not be demonstrated[5].
- The company were unable to identify a suitable response guided therapy (i.e. a rule to identify patients who benefit from treatment with ivacaftor) as all the analyses performed suggest that there is no correlation between sweat chloride levels and changes in FEV_1 improvement[5]. Therefore, the EMA stated that the indication for ivacaftor in patients with CF carrying a non-*G551D-CFTR* mutation should be based on the identification of those individual mutations for which a benefit is seen in a clinical study[5].
- Patients with severe lung disease (FEV_1 < 40% predicted) were excluded from the study[1,5,10], therefore only data for patients with mild to moderate lung disease was provided. Patients with colonisation with organisms associated with a more rapid decline in pulmonary status (e.g. *Burkholderia cenocepacia, Burkholderia dolosa*, and *Mycobacterium abscessus*) at screening were also excluded. The clinical benefit of ivacaftor in these patients is therefore uncertain.
- In the KONNECTION study, patients with non-*G551D-CFTR* mutation were followed-up four weeks after the last dose. Although CF is a chronic condition, data concerning the long-term efficacy and safety of ivacaftor in this population are lacking.
- In the KONNECTION study, although subgroup analyses were performed by age, sex, CF severity and geographical region, it is difficult to draw any meaningful conclusions as patient numbers were so small.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes a cost utility analysis (CUA) of ivacaftor that was originally undertaken to assess its cost effectiveness in the treatment of CF patients with the *G551D* mutation in the *CFTR* gene. The company asserts that this model will also reflect the cost effectiveness of ivacaftor in patients who have one of the specific non-*G551D* mutations in the *CFTR* gene listed in the licensed indication (the population of interest for the current appraisal) on the basis that outcomes in the KONNECTION study of ivacaftor[10] were similar to those observed in the STRIVE[11] and ENVISION[12] studies conducted in patients with the *G551D* mutation[1]. As there is currently no other treatment specifically licensed for CF, the analysis considers the use of ivacaftor as an adjunct to BSC compared to BSC alone. BSC is assumed to consist of CF-related medication (mainly pancreatic enzymes, dornase alfa, inhaled corticosteroids, bronchodilators, prednisone and antibiotics) and devices (oxygen vests, nebulizers and other airway clearance and respiratory devices) as per the placebo groups of the STRIVE and ENVISION studies.

A patient-level simulation model is used to estimate clinical outcomes and costs over a lifetime horizon of analysis. The modelled population characteristics are based on the patient populations in the STRIVE[11] and ENVISION[12] studies. CF patient mortality with BSC is based on UK registry data[13], and provides the basis for extrapolating the study data over time. This is done using the 48-week clinical study data in relation to gender, % predicted FEV_1, weight-for-age z scores, annual exacerbation rates and pancreatic sufficiency, which feed into risk equations linking these factors to survival, based on US registry data[14,15]. Other risk factors for which data were not available from the study (diabetes mellitus, *Staphylococcus aureus* infection, and *Burkholderia cepacia* infection) were obtained from the UK CF registry[13], and are assumed to be the same for each arm of the model.

Costs are calculated based on a costing model developed for the North of England Specialised Commissioning Group: Yorkshire and the Humber[16]. Costs of treatment have been taken from the British National Formulary (BNF)[17]. The annual ivacaftor acquisition cost is based on a confidential discount price agreed as part of a Wales Patient Access Scheme (WPAS) and is calculated based on 91% adherence, as observed in the STRIVE and ENVISION studies. This is reflected in the calculated medicine costs which are further assumed to decrease by 90% upon patent expiry in 13.5 years. The company reports that genotyping of patients is carried out as part of routine practice in the UK, and, hence, no additional tests or investigations enabling patient selection are anticipated. The utility values used in the base case model are derived from a published health-related quality of life study among British CF patient[18]. Costs and outcomes are calculated in three-month time steps, and an annual discount rate of 3.5% has been applied[1].

4.1.2 Results

The results of the base case analysis, assuming 91% adherence, a WPAS-approved confidential discount on the list price of ivacaftor, and 90% reduction in the list price following patent expiry at year 14, are presented in Table 3. The results suggest a gain of 4.9 quality-adjusted life-years (QALYs) at an additional cost of [commercial in confidence figure removed] million over the modelled lifetime, resulting in a base case incremental cost-effectiveness ratio (ICER) of [commercial in confidence figure removed] per QALY gained compared with BSC alone.

Table 3. Results of the base case analysis.

	Best supportive care plus ivacaftor	Best supportive care alone	Difference
Total costs	¶	£247,928	¶
Total life-years	17.2	11.4	**5.8**
Total QALYs	13.6	8.7	**4.9**
ICER (£/QALY gained)	¶		

¶: commercial in confidence figure removed.
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.

Key scenario analyses provided by the company are presented in Table 4. All assume 91% adherence (and consequently 91% of acquisition costs of ivacaftor), as per the base case analysis, and demonstrate the sensitivity of the modelled cost effectiveness of ivacaftor to key model assumptions.

Table 4. Results of the scenario analyses.

Scenarios	ICER	Plausibility
Rate of FEV_1 decline 50% of best supportive care	¶	Given the lack of long-term data regarding the comparative efficacy of ivacaftor plus best supportive care versus best supportive care alone, assumptions relating to the treatment benefit in the long term will be subject to uncertainty.
Rate of FEV_1 decline same as best supportive care; only benefit of ivacaftor is initial 10% absolute increase in FEV_1	¶	
Excluding the generic price assumption from the base case model	¶	AWMSG considers current list prices as relevant. This scenario therefore more relevant, particularly given the uncertainty about the future date of introduction of a generic and its expected price.

¶: commercial in confidence figure removed.
AWMSG: All Wales Medicines Strategy Group; FEV_1: forced expired volume in 1 second; ICER: incremental cost-effectiveness ratio.

4.1.3 AWTTC critique

The company assumes that outcomes assessed at 24–48 weeks for CF patients with the *G551D* mutation in the *CFTR* gene will also reflect outcomes for patients with non-*G551D* mutations. Eight week data from the KONNECTION study were similar to 24 week data in the STRIVE and ENVISION studies for surrogate outcomes such as lung function measures; however, these short term data are extrapolated over a lifetime and, as there are no survival data available for ivacaftor, these surrogate outcomes data are used to model survival, which is a key driver of the estimates of cost-effectiveness. It is therefore uncertain whether or not the modelled 5.8 years (discounted) increase in survival can be achieved in practice. The model also assumes a most favourable costing approach. Collectively, the modelled estimates of cost-effectiveness of ivacaftor in this patient population are subject to considerable uncertainty, and scenario analyses demonstrate that ICERs greater than that reported in the base case analysis may be plausible.

The company states that ivacaftor meets the AWMSG criteria for ultra-orphan medicine status (see Section 6.5).

Strengths of the economic evidence:

- Selected scenario analyses have been provided to explore the impact of key assumptions.

Limitations of the economic evidence:

- Although KONNECTION study data exists for ivacaftor in the treatment of patients with non-*G551D* mutations in the *CFTR* gene, the model relies on data from ENVISION and STRIVE studies in patients with *G551D* mutations, based on observed similarities in short-term surrogate outcomes. Based on the included mutations, the population of patients enrolled in the KONNECTION study is more heterogeneous compared with the populations of the ENVISION and STRIVE studies. There is a lack of long-term data upon which to model the long-term effectiveness of ivacaftor in any populations, and it is unclear whether long-term outcomes of ivacaftor treatment in patients with non-*G551D* mutations with be the same as in those with *G551D* mutations.
- The risk equations used to model improved survival assume constant benefit of ivacaftor over BSC in terms of FEV_1, weight gain and exacerbation rates based on 48-week data in patients with *G551D* mutations; however, the EMA noted that changes in weight cannot be attributed to lean body mass gains, and the 96-week interim analyses of PERSIST showed that there was an increase in upper respiratory tract infections (URTIs) and an increase in the incidence and duration of pulmonary exacerbations in ivacaftor-treated patients compared with 48-week data[6]. Scenario analyses demonstrate the reliance of ICER estimates on the assumed long-term effect of ivacaftor on lung function.
- The ENVISION and STRIVE trials, used to model outcomes, excluded patients with severe lung disease ($FEV_1 < 40\%$), and the model demonstrates sensitivity to the assumed lung function of patients. It is therefore uncertain that the economic evidence provided by the company would reflect the use of ivacaftor in patients with severe lung disease ($FEV_1 < 40\%$).
- The base case analysis assumes the most favourable approach to costing of ivacaftor treatment.
    - Only 91% of ivacaftor acquisition costs are included, on the basis that adherence was observed to be 91% in the clinical trials; however, in practice, the NHS may still accrue full acquisition costs regardless of the adherence level. The company also inappropriately assumes the costs of ivacaftor will decrease by 90% following patent expiry in 13.5 years, rather than adopting the prevailing NHS list or WPAS-agreed price. ICER estimates for all scenarios could be increased beyond those reported by the company.
- Only one-way scenario analyses have been provided by the company; there are several sources of uncertainty in key parameters, the combined effect of which is not explored.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have identified one published health technology assessment (HTA) of ivacaftor in the treatment of CF patients with *G551D* mutations in the *CFTR* gene[16]. This was funded by The National Institute for Health Research HTA programme, and involved adaptation of a company-provided patient-level simulation model to provide an estimate of the incremental cost per QALY gained for ivacaftor compared with BSC in the English NHS. ICERs varied across analyses in the range £335,000 and £1,274,000 per QALY gained. The authors noted the need for further evidence on the long-term effectiveness of ivacaftor[16]. No alternative published evidence specific to the use of ivacaftor in the treatment of CF patients with non-*G551D* mutations was identified.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company submission reports that, as of April 2015, [commercial in confidence figure removed] patients with relevant non-*G551D* mutations in the *CFTR* gene have been identified in NHS Wales based on company communication with lead CF clinicians (no further detail provided). Extrapolation of UK CF registry data to Wales would suggest less than one incident case per year, and therefore the company estimates the budget impact based on the [commercial in confidence figure removed] prevalent cases with non-*G551D* mutations.

The cost of ivacaftor is based on a confidential discount to its list price agreed as part of a WPAS, assuming 91% adherence (and costs).

5.1.2 Results

The company's estimates of the cost to NHS Wales of ivacaftor compared with BSC, based on [commercial in confidence figure removed] patients, assuming a WPAS-agreed discount price for ivacaftor, and assuming 91% adherence, are summarised in Table 5.

Table 5. Company-reported costs associated with use of ivacaftor for the treatment of CF.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (Indication covered in this submission)	¶	¶	¶	¶	¶
Uptake (%)	¶	¶	¶	¶	¶
Treated patients	¶	¶	¶	¶	¶
Net costs					
Medication costs	¶	¶	¶	¶	¶
Secondary & tertiary care	¶	¶	¶	¶	¶
Overall net cost	¶	¶	¶	¶	¶
¶: commercial in confidence figure removed.					

The company has provided revised estimates assuming 100% treatment adherence, which results in a net budget impact of around [commercial in confidence figure removed] per year in each of the next five years, under the WPAS-agreed discount price.

5.1.3 AWTTC critique

- Estimates of eligible patient numbers are reportedly based on known cases in NHS Wales. Clinical experts contacted by AWTTC suggested that this is an accurate reflection of the anticipated number of patients who would be eligible for treatment. The company assumes a stable population as UK registry data suggest less than once incident case per year; however, over time it is possible additional cases would accrue. As is the case for all high cost medicines, a small variation in eligible patient numbers can have a material impact on net costs.
- The company has based its net budget impact estimates on the figures included in the cost-effectiveness model, which would underestimate the budget impact:
  - Cost offsets based on reduced secondary and tertiary care resource use as included in the cost effectiveness model would not be realised as cost savings in practice without an accompanying reduction in service provision.

- The ivacaftor costs are based on the assumption of 91% adherence and only 91% of the potential (WPAS-discounted) acquisition costs. The revised figures assuming 100% of the (WPAS-discounted) acquisition costs could be more reflective of the costs to NHS Wales.

5.2 Comparative unit costs

Ivacaftor is a first-in-class medicine for the treatment of CF in patients aged six years and older with non-*G551D* mutations in the *CFTR* gene. The annual acquisition cost for ivacaftor in Wales is [commercial in confidence figure removed], based on a confidential discount price agreed as part of a WPAS and the licensed dose of 150 mg twice-daily. There are no other comparator treatments available for this licensed indication.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 12 and 13 May 2015.
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

The applicant company suggests that ivacaftor is an ultra-orphan medicine[19]. Ivacaftor is designated by the EMA Committee for Orphan Medicinal Products as an orphan medicine[20], and in the previous AWMSG appraisal of ivacaftor for the treatment of CF patients aged six years and older who have a *G551D* mutation in the *CFTR* gene, ivacaftor was considered as an ultra-orphan medicine. The current AWMSG policy for appraising orphan, ultra-orphan and rare-disease medicines defines an ultra-orphan medicine as a medicine that has been granted EMA designated orphan status and is used to treat a condition with a prevalence of 1 in 50,000 or less in the UK (or 60 patients in Wales)[19]. This definition applies to the full population of the licensed indication. The prevalence of CF is estimated to be 3.5 in 50,000[20], which equates to around 210 patients in Wales. Gating mutations are present in approximately 5% of the CF patient population worldwide and in the EU; in Wales this would suggest a population of around 11 patients. There are [commercial in confidence figure removed] patients with *G551D* gating mutation currently receiving treatment in Wales and a further [commercial in confidence figure removed] patients with a non-*G551D* gating mutation in Wales.

AWTTC consider ivacaftor to be eligible to be appraised as an ultra-orphan medicine as it has EMA orphan status and 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).

Should NMG/AWMSG consider ivacaftor as an ultra-orphan medicine and the cost per QALY is above the normal thresholds applied, additional criteria for appraising these medicines will be considered (see Table 6).

Table 6. 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)	There are currently no other treatments for CF in patients with non-*G551D* mutations that targets the underlying cause of CF.
Whether the medicine can reverse or cure, rather than stabilise 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	Not applicable.
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)	Specific evidence not provided
Added value to the patient's family (e.g. impact on a carer or family life)	Specific evidence not provided
BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire Revised; *CFTR*: cystic fibrosis transmembrane conductance regulator; FEV_1: forced expiratory volume in one second (see Glossary).	

GLOSSARY

BMI-for-age z-score
A body mass index (BMI) z-score or standard deviation score indicates how many units (of the standard deviation) a child's BMI is above or below the average BMI value for their age group and sex. For instance, a z-score of 1.5 indicates that a child is 1.5 standard deviations above the average value, and a z-score of −1.5 indicates a child is 1.5 standard deviations below the average value[21].

CFQ-R
The cystic fibrosis questionnaire-revised (CFQ-R) is a disease-specific, patient-reported outcome measure of health-related quality of life[22].

FEV_1
The forced expired volume in one second is the volume of air that can be expelled from maximum inspiration in the first second[23].

Percent of predicted FEV_1
FEV1 expressed as a percentage of a predicted value, calculated using a reference population[24].

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