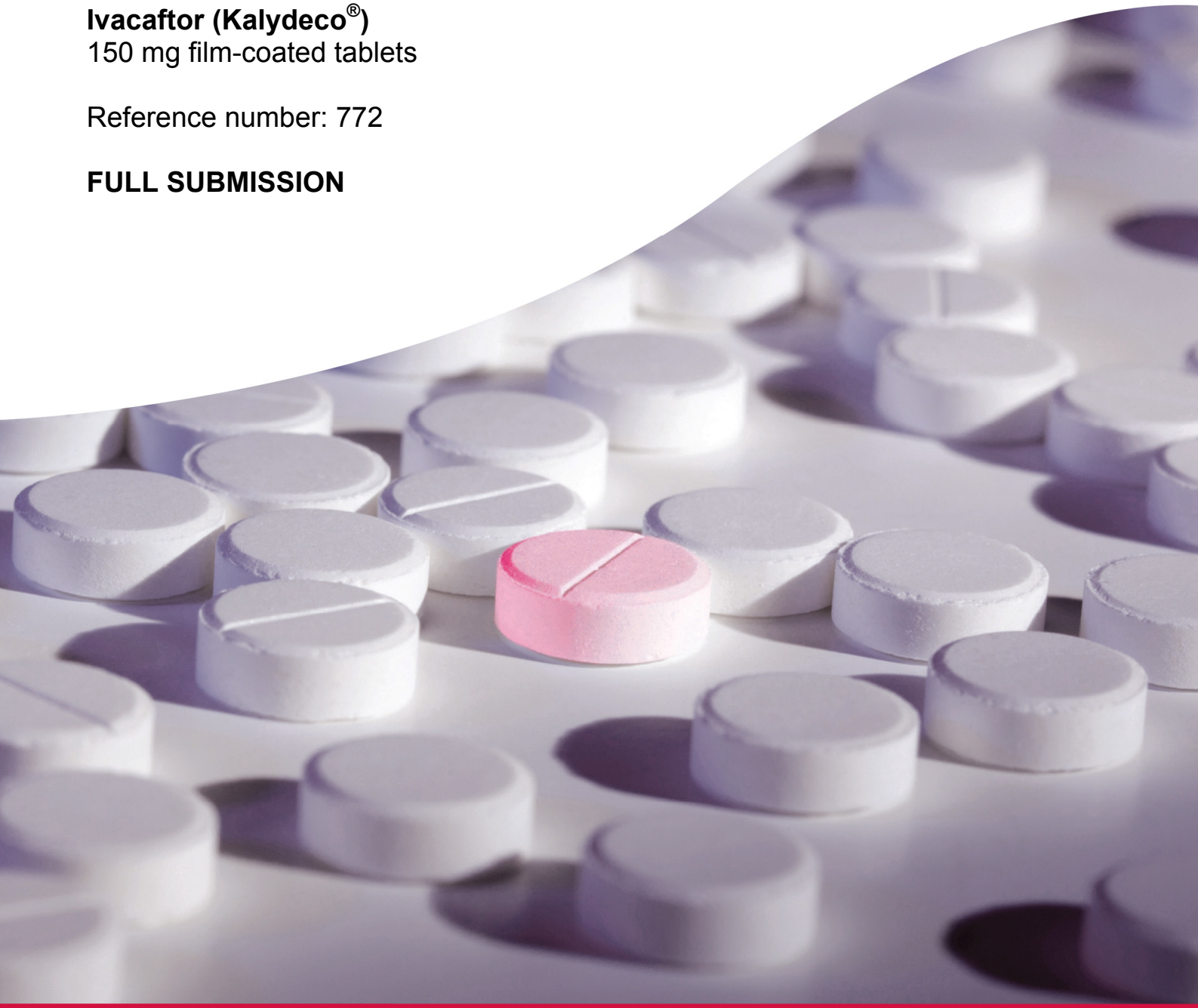
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Ivacaftor (Kalydeco®)
150 mg film-coated tablets

Reference number: 772

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 23 November 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Ivacaftor (Kalydeco®) is indicated for the treatment of cystic fibrosis in patients aged six years and older who have a *G551D* mutation in the *CFTR* gene[2].
Dosing	The recommended dose is 150 mg taken orally every 12 hours[2].
Marketing authorisation date	23 July 2012[2]

2.0 DECISION CONTEXT

2.1 Background

Cystic fibrosis (CF) is the most common recessively inherited genetic condition in the UK with an incidence of approximately 1 in 2,500 live births[3]. Data from the UK CF Registry stated that, as of 2010, there were 366 people in Wales diagnosed with CF[4]. CF is a chronic and life-threatening condition, affecting respiratory and digestive function[5]. Chronic lung infections, intense airway inflammation and progressive lung disease are the major cause of high morbidity and mortality in CF[5]. Due to the variability in the course of the disease, it is difficult to provide an accurate prognosis. The median life expectancy in 2008 was 37.4 years[6]; however, a study of CF mortality and survival in the UK between 1947 and 2003 concluded that previous predictions of a mean survival of > 50 years of age for infants with CF recently born in the UK appear realistic, and that survival with CF continues to improve[7].

The condition is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which encodes a protein channel that is essential for the regulation of salt and water movements across cell membranes[3]. Disruption of CFTR channel function results in thickened secretions in organs with epithelial cell lining, affecting most critically the lungs, but also the digestive system and vas deferens. The presence of abnormally viscous mucus in the lungs interferes with the clearance of micro-organisms from the airways, resulting in life-threatening manifestations that persist over the patient's lifetime[1]. More than 1,500 *CFTR* mutations that cause CF have been identified[8].

Current CF therapy aims to alleviate symptoms of the condition, and includes infection control, respiratory care and nutritional care[3]. Ivacaftor (Kalydeco®) is a first-in-class CFTR potentiator that offers a new therapeutic approach to the treatment of CF, by addressing the underlying protein defect in patients with a mutation in the *G551D* region of the *CFTR* gene. A *G551D* mutation results in defective CFTR channel opening[8], and, based on 2010 data, is estimated to represent 5.7% of CF mutations[4]. Ivacaftor increases the channel activity of *G551D*-mutated CFTR, improving the transport of chloride ions across cell membranes[8]. The exact mechanism for this activity has not been elucidated[2].

2.2 Comparators

The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was best supportive care.

2.3 Guidance and related advice

- Cystic Fibrosis Trust. Standards for the clinical care of children and adults with cystic fibrosis in the UK (2011)[3].
- Kerem et al. Standards of care for patients with cystic fibrosis: a European consensus (2005)[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

Two phase III trials, STRIVE and ENVISION, have been conducted to evaluate the efficacy and safety of ivacaftor in adult and paediatric CF patients, respectively, with the *G551D* mutation on at least one *CFTR* allele[1,10–12]. An open-label extension of the STRIVE and ENVISION trials (PERSIST), designed to evaluate the safety of long-term (96 weeks) ivacaftor treatment, is ongoing and is highlighted below; however, data from this study are currently limited[1].

Results from a phase IIb study of ivacaftor for patients with a *ΔF508* mutation on both alleles of the *CFTR* gene (DISCOVER) have been included in a pooled safety analysis only[1,13]. The company submission also provides detail for a phase II pharmacokinetics study and a systematic review of symptomatic treatments for CF versus placebo[1,14]. These are of limited relevance to the indication under consideration and are therefore not discussed further.

3.1 STRIVE and ENVISION studies

STRIVE and ENVISION were multicentre, randomised, double-blind, placebo-controlled phase III trials designed to evaluate the efficacy of ivacaftor in subjects with mild to moderate CF and a *G551D* mutation in at least one *CFTR* allele[1,10–12]. STRIVE enrolled 161 patients aged 12 years and older with forced expiratory volume in one second (FEV_1; see Glossary) of 40–90% of predicted. ENVISION enrolled 52 patients aged 6–11 years with FEV_1 of 40–105% of predicted. Patients were randomised 1:1 to ivacaftor 150 mg or placebo, which were administered every 12 hours. Double-blinded treatment was administered for 48 weeks, with the primary analysis performed at 24 weeks. All patients remained on their current background treatment regimen, i.e. best supportive care, consisting of pancreatic enzymes, dornase alfa, inhaled corticosteroids, bronchodilators, prednisone, antibiotics and devices (oxygen vests, nebulisers and other airway clearance and respiratory devices)[1,10–12].

The primary endpoint was absolute change in the percent of predicted FEV_1 (see Glossary) from baseline at 24 weeks. For the STRIVE study, this endpoint showed an increase of 10.4 percentage points in the ivacaftor arm versus a decrease of 0.2 percentage points in the placebo arm; the absolute difference between treatment arms was therefore 10.6 percentage points (95% confidence interval [CI]: 8.57, 12.6; $p < 0.001$)[12]. For the ENVISION study, the primary endpoint showed an increase of 12.6 percentage points in the ivacaftor arm versus an increase of 0.1 percentage points in the placebo arm, with an absolute difference of 12.5 percentage points (95% CI: 6.56, 18.3; $p < 0.0001$)[11]. These figures were supported by statistically significant results for secondary endpoints including absolute change in the percent of predicted FEV_1 from baseline at 48 weeks, relative risk of pulmonary exacerbation (measured in STRIVE only), mean absolute change from baseline in body weight and absolute change from baseline in sweat chloride. The mean absolute change from baseline in cystic fibrosis questionnaire-revised (CFQ-R) respiratory domain score (see Glossary), though only statistically significant from STRIVE, was also supportive (see Appendix 1, Table 1A)[1,12].

3.2 PERSIST study

The PERSIST study is an ongoing 96-week, open-label extension for all participants of the STRIVE and ENVISION studies, designed to evaluate the long-term safety of ivacaftor treatment in subjects with CF. Data from an interim analysis at 48 weeks have been provided[1].

Patients that were intolerant to ivacaftor in the STRIVE or ENVISION studies were excluded. Patients (n = 192) received open-label ivacaftor 150 mg every twelve hours and remained on their current background treatment regimen. At the interim analysis at week 48, patients from the STRIVE study had completed 48 weeks of open-label ivacaftor (total 96 weeks), whereas patients from ENVISION had completed 24 weeks of open-label ivacaftor (total 72 weeks). The primary endpoint was safety; the results for which are included in a pooled analysis discussed in Section 3.3. Efficacy parameters were analysed as secondary endpoints of the PERSIST study and were supportive of STRIVE and ENVISION: the absolute change in percent predicted FEV_1 observed in the STRIVE study was sustained in patients that had previously received ivacaftor (10.3 percentage points) and elevated to similar levels for those that had previously received placebo (9.5 percentage points) through week 48 of PERSIST. Similarly, the absolute change in percent predicted FEV_1 observed in the ENVISION study was sustained in patients that had previously received ivacaftor (10.0 percentage points) and was elevated, but to a slightly lower extent, for those that had previously received placebo (8.0 percentage points) through week 24 of PERSIST. The body weight gain observed in STRIVE and ENVISION was maintained[1,8].

The rate and duration of pulmonary exacerbations was less in the 48-week treatment period of STRIVE (25 subjects had 41 events; mean duration: 11.6 days) than in the 48-week open-label treatment period of PERSIST (38 subjects had 64 events; mean duration: 19.8 days). Pulmonary exacerbation was not measured as a secondary endpoint in ENVISION[1].

3.3 Pooled safety analysis

Due to the orphan nature of CF and the limited trial populations, the company provided pooled safety analyses of the STRIVE, ENVISION, PERSIST and DISCOVER studies[1]. Of all subjects that received ivacaftor in the pooled phase IIb/III studies (STRIVE, ENVISION, PERSIST and DISCOVER; n = 293), 89.8% experienced an adverse event (AE). In the pooled placebo-controlled studies (STRIVE, ENVISION and DISCOVER; n = 353 [ivacaftor: n = 221; placebo: n = 132]), 92.5% of the ivacaftor group and 97.0% of the placebo group experienced AEs, of which 33.5% and 34.1%, respectively, were deemed to be treatment-related. The most commonly reported AEs were cough, CF lung (pulmonary exacerbation), headache, dizziness, upper respiratory tract infection (URTI) and rash. AEs that were more commonly reported in ivacaftor-treated patients than in those that received placebo included cough, headache, URTI, rash, dizziness and identification of bacterial sputum (see Appendix 1, Table 1B). In addition, 39 (17.6%) patients experienced a serious AE (SAE) in the ivacaftor group, versus 46 (34.8%) in the placebo group. The most common SAE was CF lung (23 [10.4%] for ivacaftor versus 35 [26.5%] for placebo). Four (1.8%) patients withdrew from ivacaftor treatment due to AEs: one for arthritis, one for myopathy, one for asthenia, fatigue and headache, and one for hepatic enzyme increase. There were no deaths reported[1,8].

3.4 AWTTC critique

- Ivacaftor is a first-in-class medicine; there is currently no other licensed therapy that addresses the underlying molecular cause of CF.
- Results from STRIVE, ENVISION and PERSIST suggest that ivacaftor has a significant, sustained beneficial effect on clinically relevant outcomes (i.e. increased FEV_1, weight gain and decreased rate of pulmonary exacerbations) for patients with CF that have a *G551D* mutation, at least up to 60 weeks[8]. FEV_1 is the accepted primary clinical endpoint for efficacy studies in CF[15].
- Studies provided in the company submission included patients with mild to moderate CF only. Patients with severe lung disease, defined as FEV_1 < 40%, were excluded due to the greater likelihood of the presence of structural, irreversible damage to the bronchioles. Therefore, no data for the efficacy or safety of ivacaftor treatment in patients with severe CF are reported in the company submission. The European Medicines Agency (EMA) reports that there are results from a limited number of patients with an FEV_1 < 40% and that these are consistent with those seen in the overall population. However the EMA caution drawing any sound conclusions due to the very limited number of patients analysed[8]. Patients with unstable CF (e.g. those colonised with organisms associated with a more rapid decline in pulmonary status, and those with recent acute upper or lower respiratory infection, pulmonary exacerbation or change in therapy) were also excluded from STRIVE and ENVISION.
- The EMA noted an increased incidence and duration of pulmonary exacerbations in ivacaftor-treated patients from the STRIVE study during PERSIST. Due to this, longer-term follow up was deemed necessary. Data from the completed PERSIST study and a planned five-year observational study are expected to conclude whether the effect of ivacaftor is maintained over time; this is of particular importance due to the chronic nature of CF[8].
- Treatment with ivacaftor appears to be well tolerated; however, safety data are currently only available for a total of 96 weeks for 144 patients (from STRIVE and PERSIST). In addition, safety data for the paediatric population are very limited: only 23 patients aged 6–11 years were included in the pooled analysis of the phase IIb/III studies (all were from ENVISION). The EMA stated that safety data in these 23 subjects seem not to be different to those older than 12 years. The EMA noted increased reporting of sputum bacteria and URTIs in patients that received ivacaftor during PERSIST, which has been reflected in the Summary of Product Characteristics (SPC)[2]. The company have committed to addressing these issues with additional pharmacovigilance activities, including the publication of 96-week data from PERSIST and a five-year observational study, including microbiological and clinical endpoints[8].
- The studies provided compare ivacaftor as an adjunct therapy to best supportive care with placebo plus best supportive care. It was noted that patients in the placebo arm of STRIVE received a higher number of concomitant medications at the start of the study; however the results remained favourable towards ivacaftor[1,2,8].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost utility analysis (CUA) of ivacaftor in its licensed indication for the treatment of CF in patients aged six years and older who have a *G551D* mutation in the *CFTR* gene[1]. There is currently no licensed treatment for CF; hence the analysis considers the use of ivacaftor as an adjunct therapy to best supportive care compared to best supportive care only. Best supportive care is considered to consist of CF-related medication (mainly pancreatic enzymes, dornase alfa, inhaled corticosteroids, bronchodilators, prednisone and antibiotics) and devices (oxygen vests, nebulisers and other airway clearance and respiratory devices). These are the modalities used in the randomised, double blind, placebo controlled phase III studies STRIVE and ENVISION[11,12].

A patient-level simulation model is used to estimate clinical outcomes and costs over a lifetime analytical time horizon. The modelled population characteristics are based on the patient populations in the STRIVE and ENVISION trials, which are considered broadly representative of the target population in Wales, based on a comparison with UK CF Trust registry data[4]. CF patient mortality with best supportive care is based on this UK registry data, and provides the basis for extrapolating the trial data over time. This is done using the 48-week clinical trial 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[16,17]. Other risk factors for which data were not available from the trial (diabetes mellitus, *Staphylococcus aureus* infection, and *Burkholderia cepacia* infection) were obtained from the UK CF registry, and are assumed to be the same for each arm of the model[4].

Costs are calculated based on a costing model developed for the North of England Specialised Commissioning Group: Yorkshire and the Humber[18]. Costs of treatment have been taken from the British National Formulary (BNF)[19]. 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 (overall study drug compliance rate at 48 weeks defined as the ratio of the number of tablets consumed to the expected number of tablets to be administered during the treatment period) as observed in the clinical trials of ivacaftor[20]. This is reflected in the calculated drug costs, which are further assumed, contrary to AWMSG guidance[21], to decrease by 90% upon patent expiry in 14 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 utilities used in the model are based on data collected during the ivacaftor clinical trials. Sensitivity analyses assuming alternate utility values from a UK study by Gee et al and an ongoing National Institute for Health and Clinical Excellence (NICE) health technology assessment (being carried out by the School of Health and Related Research [ScHARR] at the University of Sheffield) of colistimethate sodium have been provided[22,23]. 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 a WPAS-approved confidential discount, 91% adherence and 90% reduction in costs following patent expiry at year 14, are presented in Table 1. The results suggest a gain of 5.7 quality-adjusted life-years (QALYs) compared with best supportive care. Additional information provided as commercial in confidence.

Table 1. Results of the base case analysis

	Best supportive care + ivacaftor	Best supportive care only	Difference
Total costs	*	£247,928	*
Total life-years	17.2	11.4	**5.8**
Total QALYs	16.4	10.7	**5.7**
ICER (£/QALY gained)	*		
ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year			

*commercial in confidence data provided

The company provided results for subgroup analyses based on gender, age and FEV_1 severity. These show that ivacaftor plus best supportive care has more favourable ICERs for males, younger age groups and milder FEV_1 severity. Additional information provided as commercial in confidence.

Key scenario analyses provided by the company are presented in Table 2. All assume 91% adherence and a 90% cost reduction with generic ivacaftor, as per the base case analysis.

Table 2. Results of the scenario analyses

Scenarios	ICER	Plausibility
Scenario 1 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.
Scenario 2 Rate of FEV_1 decline same as best supportive care; only benefit of ivacaftor is initial 10% absolute increase in FEV_1	*	
Scenario 3 Using utilities from Gee et al 2002[22]	*	Plausible. Utilities used in the base case appear to be overestimated. The study by Gee et al is UK-based. There is good level of agreement between its utilities and those reported in the ScHARR/NICE colistimethate sodium health technology appraisal.
Scenario 4 Using utilities from the ScHARR/NICE colistimethate sodium health technology appraisal[23]	*	
Scenario 5 Excluding the generic price assumption from the base case model	*	AWMSG considers current list prices as relevant[21]. Plausible given the uncertainty about the future date of introduction of a generic and its expected price.
AWMSG: All Wales Medicines Strategy Group; FEV_1: forced expired volume in 1 second; ICER: incremental cost-effectiveness ratio; NICE: National Institute of Health and Clinical Excellence; ScHARR: School of Health and Related Research		

*commercial in confidence data provided

Sensitivity analyses examining the impact of changing the survival curve parameters and the survival model coefficients are also presented. The impact of population variability is also explored using bootstrapping. The sensitivity analyses results are reported in terms of the impact of changing the parameters of interest on the predicted additional survival associated with ivacaftor, rather than ICER estimates.

4.1.3 AWTTC critique

Whereas the available clinical evidence for ivacaftor is limited to 48 weeks, the base case model assumes continuous benefit over a lifetime. However, interim analyses of an open-label extension study (PERSIST) suggest the effect on several endpoints at 96 weeks is slightly decreased compared with those attained at 48 weeks; in particular the incidence and duration of pulmonary exacerbations and URTIs, which are used in the risk equations to model survival improvement, are higher. It is therefore uncertain whether the life-long continued benefit as modelled would be achieved in practice. Moreover, there are no data on the assumed (modelled) benefits in survival, which are the key economic driver. The model also assumes a most favourable costing approach. Although the cost-effectiveness of ivacaftor in this patient population is subject to considerable uncertainty, there is certainty that the ICER for ivacaftor exceeds conventional thresholds of cost-effectiveness. Sensitivity and scenario analyses demonstrate that ICERs greater than that reported in the base case analysis may be plausible.

Strengths of the economic evidence:

- Direct comparative data for ivacaftor as an add-on therapy for up to 48 weeks are available from two randomised controlled trials in the licensed indication population.
- A range of sensitivity and scenario analyses have been provided to explore uncertainty in key parameters.

Limitations of the economic evidence:

- There is a lack of long-term data upon which to model the long-term effectiveness of ivacaftor. The risk equations used to model improved survival assume constant benefit of ivacaftor over best supportive care in terms of FEV_1, weight gain and exacerbation rates based on 48 week data; 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 URTIs and an increase in the incidence and duration of pulmonary exacerbations in ivacaftor-treated patients compared with 48 week data[8]. Sensitivity and scenario analyses demonstrate that results are sensitive to the assumptions relating to the long-term effect of ivacaftor on lung function.
- The ENVISION and STRIVE trials excluded patients with severe lung disease (FEV_1 < 40%), and the model demonstrates sensitivity to the assumed lung function of patients.
- The utility values assumed in the base case model are based on EQ-5D data collected in the STRIVE trial, which was conducted in patients aged 12 years and older, and are assumed to be applicable to children aged six years of age. In addition, the utility values assumed in the model appear to be higher than population norms. Scenario analysis using alternative, plausible utility values resulted in less favourable ICER values compared with the base case analysis.
- 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 has provided no analyses assuming 100% acquisition costs; AWTTC-conducted analyses indicate the base case ICER increases when full acquisition costs are assumed. ICER estimates for all other scenarios would also be increased beyond those reported by the company. In addition, the company assumes the costs of ivacaftor will decrease by 90% in year 14 following patent expiry; however, AWMSG considers current lists prices as relevant[21], as per Scenario 5 in Table 2.
- It is assumed that ivacaftor will be used only in patients who are already screened for the presence of the *G551D* mutation.

- Only one-way sensitivity and scenario analyses have been provided by the company; however, 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 not identified any published evidence on the cost-effectiveness of ivacaftor within its current licensed indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on 2010 data from the UK CF registry on CF prevalence in Wales, and expected annual growth figures, the company estimates that there are 395 CF patients in Wales as of 2012[4]. The company reports that 5.7% of CF patients carry the *G551D* mutation, and an estimated 16.5% of those are < 6 years of age, therefore would not be eligible for treatment. Based on the estimated population in Wales in 2012, there would be 19 patients ≥ 6 years of age that would be eligible for treatment with ivacaftor.

5.1.2 Results

The company anticipates an incremental cost resulting from using ivacaftor as an add-on to best supportive care. The incremental costs, based on a WPAS-agreed discount price for ivacaftor, are summarised in Table 3. Additional information provided as commercial in confidence.

Table 3. Company-reported costs associated with use of ivacaftor for the treatment of CF

*commercial in confidence data provided

	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
Number of eligible patients (Indication covered in this submission)	20	20	21	22	23
Uptake (%)	100	100	100	100	100
Treated patients	20	20	21	22	23
Net costs					
Medication costs	*	*	*	*	*
Administration and monitoring	N/A	N/A	N/A	N/A	N/A
Primary care	N/A	N/A	N/A	N/A	N/A
Secondary & tertiary care	-£48,828	-£55,829	-£63,305	-£71,285	-£79,795
Staffing	N/A	N/A	N/A	N/A	N/A
Infrastructure	N/A	N/A	N/A	N/A	N/A
Personal social services	N/A	N/A	N/A	N/A	N/A
Overall net cost	*	*	*	*	*

5.1.3 AWTTC critique

- The company has made a reasonable effort to characterise the epidemiology and treatment options of CF using UK and Wales-specific data. However, there is uncertainty around the estimated prevalence of *G551D* mutation in the *CFTR* gene and, hence, around the reported number of eligible patients.
- The budget impact estimates provided do not take into account mortality in this patient population.
- The company has based its total cost estimates on the cost-effectiveness model. Therefore, the limitations of the cost-effectiveness model feed through to the budget impact estimates. The costs of regular liver function monitoring (recommended in the ivacaftor SPC[2]) and initial genotyping of patients where these data are not available are not included in the budget impact calculations. Furthermore, it is assumed that the observed adherence of 91% will result in only 91% of the annual acquisition costs being accrued, which may not be the case in practice. The net financial costs of introducing ivacaftor in practice may not be equivalent to the opportunity costs calculated for the economic analysis.
- Collectively, the budget impact calculations are subject to uncertainty.

5.2 Comparative unit costs

Ivacaftor is a first-in-class drug for the treatment of CF in patients aged six years and older and have a *G551D* mutation in the *CFTR* gene. The 2013 annual acquisition cost for ivacaftor in Wales is 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 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, ivacaftor (Kalydeco®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company highlighted that the PERSIST study is scheduled for completion in May 2013. No other studies for the indication under consideration are currently underway[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Dates of evidence search: 8, 19 and 20 November 2012
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to ultra-orphan medicines

The applicant company suggests that ivacaftor is an ultra-orphan medicine. During its meeting of 12 and 13 June 2012, the Committee for Orphan Medicinal Products recommended that the orphan designation of the medicine be maintained, as the prevalence, based on recent analyses, was estimated to be approximately 0.7 people in 10,000[24].

Ultra-orphan medicines are orphan drugs that are licensed for the treatment of diseases with a prevalence of less than 1 in 50,000 persons in the European Union at the time of submission of the designation application to the EMA. Since the prevalence of CF is estimated to be 3.5 in 50,000, it is suggested that ivacaftor does not meet the AWMSG criteria for ultra-orphan status.

GLOSSARY

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[15].

Percent of predicted FEV_1
FEV_1 expressed as a percentage of a predicted value, calculated using a reference population[25].

CFQ-R
The cystic fibrosis questionnaire-revised (CFQ-R) is a disease-specific, patient-reported outcome measure of health-related quality of life[26].

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Appendix 1. Additional clinical information

Table 1A. Additional clinical information from STRIVE and ENVISION[1,10–12]

Endpoint	Time point	STRIVE		ENVISION	
		Treatment difference*	p value	Treatment difference*	p value
Absolute change from baseline in percent predicted FEV_1 (%)	Week 24	10.6†	< 0.0001	12.5†	< 0.0001
	Week 48	10.5§	< 0.0001	10.0§	0.0006
Absolute change from baseline in pooled-respiratory CFQ-R score	Week 24	8.1§	< 0.0001	6.1§	0.1092
	Week 48	8.6	< 0.0001	5.1	0.1354
Absolute change from baseline in sweat chloride (mMol/l)	Week 24	−47.9§	< 0.0001	−54.3§	< 0.0001
	Week 48	−48.1	< 0.0001	−53.5	< 0.0001
Relative risk of pulmonary exacerbation (hazard ratio)	Week 24	0.40	0.0016	¶	¶
	Week 48	0.46§	0.0012	¶	¶
Absolute change from baseline in body weight (kg)	Week 24	2.8	< 0.0001	1.9§	0.0004
	Week 48	2.7§	0.0001	2.8	0.0002

CFQ-R: cystic fibrosis questionnaire-revised; FEV_1: forced expired volume in one second
* Treatment difference = effect of ivacaftor − effect of placebo
† Pre-specified primary endpoint
§ Pre-specified secondary endpoint
¶ Not measured

Table 1B. Adverse events with an incidence of at least 5% in either treatment arm in the pooled placebo-controlled studies (STRIVE, ENVISION and DISCOVER)[1,8]

Adverse event	Ivacaftor (n = 221) n (%)	Placebo (n = 132) n (%)
Cough	74 (33.5)	55 (41.7)
CF lung	65 (29.4)	68 (51.5)
Headache	37 (16.7)	19 (14.4)
URTI	35 (15.8)	16 (12.1)
Nasal congestion	35 (15.8)	17 (12.9)
Oropharyngeal pain	34 (15.4)	22 (16.7)
Pyrexia	25 (11.3)	18 (13.6)
Productive cough	23 (10.4)	17 (12.9)
Nausea	23 (10.4)	12 (9.1)
Rash	23 (10.4)	7 (5.3)
Abdominal pain	21 (9.5)	14 (10.6)
Diarrhoea	20 (9.0)	12 (9.1)
Nasopharyngitis	20 (9.0)	12 (9.1)
Abdominal pain upper	17 (7.7)	13 (9.8)
Fatigue	17 (7.7)	12 (9.1)
Sinusitis	16 (7.2)	11 (8.3)
Vomiting	15 (6.8)	17 (12.9)
Rales	14 (6.3)	12 (9.1)
Haemoptysis	13 (5.9)	18 (13.6)
Rhinitis	13 (5.9)	4 (3.0)
Dizziness	12 (5.4)	3 (2.3)
Arthralgia	11 (5.0)	6 (4.5)
Rhinorrhoea	11 (5.0)	12 (9.1)
Wheezing	11 (5.0)	7 (5.3)
Bacteria sputum identified	11 (5.0)	5 (3.8)
Respiratory tract congestion	9 (4.1)	9 (6.8)
CF: cystic fibrosis; URTI: upper respiratory tract infection		