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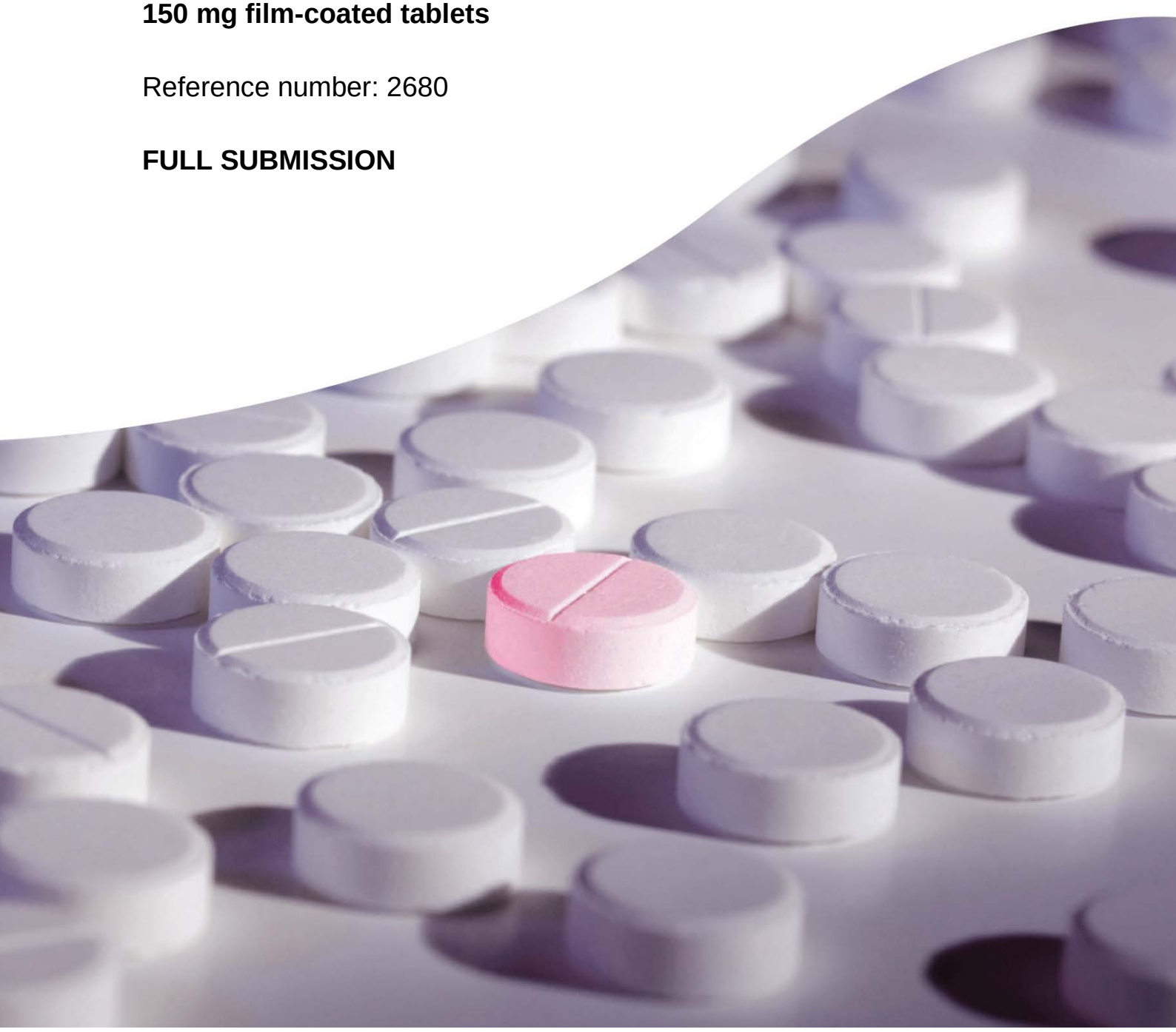
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Ivacaftor (Kalydeco®)
150 mg film-coated tablets

Reference number: 2680

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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This report should be cited as:
All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Ivacaftor (Kalydeco®) 150 mg film-coated tablets. Reference number:2680. February 2017.

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

This assessment report is based on evidence submitted by Vertex Pharmaceuticals (Europe) Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	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. ▼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. 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 with fat-containing food[2].
Marketing authorisation date	Date of licence extension: 16 November 2015[3]. Licensed on 23 July 2012 for the treatment of CF in patients age six years and older and weighing 25 kg or more who have a *G551D* gating (class III) mutation in the *CFTR* gene. Extension on 28 July 2014 to include additional gating mutations in the following *CFTR* gene: *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R*[3].

2.0 DECISION CONTEXT

2.1 Background

Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting approximately one 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]. CF dramatically shortens life expectancy: in 2015 the UK median age at death for patients with CF was 28 years of age[6].

More than 1,500 *CFTR* mutations that cause CF have been identified, but the functional importance is known only for a small number[5]. The *R117H-CFTR* mutation, reported to be present in 3% of CF patients in Wales[6], causes impaired *CFTR*-channel conductance and reduced channel gating with the latter being the main defect[7]. Patients with *R117H-CFTR*, have a reduced median life expectancy of 50 years with a median age of death being 32 years in the UK[5]. Based on limited data, *CFTR* mutations associated with a less severe phenotype appear to result in a disease process that is approximately ten years slower than for CF patients with severe disease[5]. Historically, many individuals with an *R117H-CFTR* mutation were not diagnosed with CF until later childhood or adult years when the disease had progressed; this has changed recently because of advances in newborn screening for *CFTR* mutations[5].

The *R117H* mutation is associated with variable disease expression ranging from normal to CF[5]. The function of *R117H* depends on which polythymidine ([poly-T]: 5T, 7T or 9T) form is present in the same copy of the *CFTR* gene with *R117H*[5]. The *R117H* mutation with the 5T variant typically results in more severe CF than the *R117H* mutation with the 7T variant[5]. Although many patients with the 7T variant will not have CF lung disease, some cases of severe disease have been reported[5]. The 9T variant is highly unlikely to cause symptoms of CF disease[5]. Although the *R117H-CFTR* mutation is associated with progression in lung function decline with age, the severity of CF per age group is generally less than that caused by the *G551D-CFTR* mutation or other *CFTR* mutations associated with a severe phenotype[5].

Patients with an *R117H-CFTR* mutation are currently managed with standard of care (SoC) treatments that do not address the underlying cause of disease[1]. Treatments aim to alleviate symptoms of the condition and include daily prophylactic medications and supplements such as pancreatic enzymes, nutritional and vitamin supplements, oral or nebulised antibiotics, nebulised mucolytic agents, steroids, bronchodilators and daily physiotherapy[1]. Ivacaftor is a type of *CFTR* modulator known as a *CFTR* potentiator, which increases channel gating and consequently improves chloride transport[5]. It is the first and only licensed *CFTR* potentiator targeting the underlying cause of disease and is intended for use as an adjunct to SoC[1].

2.2 Comparators

The comparator included in the company submission was SoC treatments.

2.3 Guidance and related advice

- Welsh Health Specialised Services Committee. Specialised services policy: ivacaftor (Kalydeco®) for CF (*G551D* and specific other non *G551D* mutations) (2016)[8].
- Smyth AR, Bell SC, Bojcin S, et al. European CF Society standards of care: best practice guidelines (2014)[9].
- Royal Brompton & Harefield CF Centre. Clinical guidelines: care of adults with CF (2013)[10].
- CF Trust. Standards for the clinical care of children and adults with CF in the UK (2011)[4].
- Karem E, Conway S, Elborn S, et al. Standards of care for patients with CF: a European consensus (2005)[11].

A recommendation has been issued for the use of ivacaftor (Kalydeco®) film-coated tablets within NHS Wales for the treatment of CF in patients age six years and older who have one of the following gating (class III) mutations in the CFTR gene: *G551D*[12], *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R*[13]. Subsequent to AWMSG recommendation, this medicine has been made available in Wales.

A recommendation has been issued for the use of ivacaftor (Kalydeco®) granules by AWMSG for the treatment of CF in children aged two to less than six years weighing less than 25 kg who have one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R*[14].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of one phase III study, KONDUCT, and interim data analysis from an ongoing extension study, KONTINUE, to evaluate the efficacy and safety of ivacaftor in patients with CF and with an *R117H-CFTR* mutation[1,7].

3.1 KONDUCT and KONTINUE

KONDUCT was a multicentre, phase III randomised, double-blind, placebo-controlled, parallel-group study conducted in 69 patients ≥ six years of age with CF who had a *R117H-CFTR* mutation on at least one allele[7]. All patients had a percentage of predicted forced expiratory volume in one second (percent predicted FEV_1: see Glossary) of at least 40%[7]. The majority of patients were aged ≥ 18 years; 24 patients were enrolled onto ivacaftor and 26 patients were enrolled onto placebo. Most patients (87%) were confirmed pancreatic sufficient based on faecal elastase concentrations of ≥ 200 µg[7]. Baseline body mass index (BMI) in both groups was considered in the normal range[7]. Patients were allowed concomitant medications and supplements typical of a CF population[1]. Patients were assigned 1:1 to receive placebo or ivacaftor 150 mg every 12 hours for 24 weeks[7]. Randomisation was stratified by age (6–11, 12–17, and ≥ 18 years) and percent predicted FEV_1 (< 70, ≥ 70 to ≤ 90, and > 90)[7]. The primary outcome was the absolute change from baseline in percent predicted FEV_1 through week 24[7]. Secondary outcomes included safety, changes in sweat chloride concentrations, time-to-first pulmonary exacerbation, and CF Questionnaire-Revised (CFQ-R) respiratory domain scores[7]. A total of 65 patients who completed KONDUCT were enrolled in the KONTINUE study, after a three-week washout period and then received open-label ivacaftor 150 mg every 12 hours for up to 104 weeks[7]; the company have provided interim data analysis at week 12[1].

Analyses were conducted for the overall population and pre-specified subgroups based on age category[7], however only results for the adult population (≥ 18 years) will be reported to reflect the licensed indication: see Table 1 for a summary of the results. Treatment with ivacaftor resulted in a mean absolute change in percent predicted FEV_1 through week 24 of 4.51 percentage points in the ivacaftor group versus −0.46 percentage points in the placebo group[2,5,7]. The estimated treatment difference for ivacaftor (n = 24) versus placebo (n = 26) was 4.96 percentage points (95% confidence interval [CI]: 1.15 to 8.78; p = 0.01)[2,5,7]. Patients without *Pseudomonas aeruginosa* (*Pa*) infection at baseline had a slightly larger treatment difference in favour of ivacaftor compared to placebo than subjects with *Pa* infection at baseline (infected: 4.32 percentage points, [commercial in confidence data removed]; not infected: 5.73 percentage points)[5] [commercial in confidence text and data removed][15].

For all adults, the mean change at week 24 from baseline in sweat chloride in the placebo group was −4.01 mmol/l and −25.89 mmol/l in the ivacaftor group: treatment difference between groups was −21.87 mmol/l (95% CI: −26.46 to −17.28; p < 0.0001)[5,7]. Significant mean changes were also observed in the pooled respiratory domain of the CFQ-R at week 24 (placebo: −0.46; ivacaftor: 12.18): treatment difference was 12.64 (95% CI: 5.02 to 20.25; p = 0.0017)[5,7]. There were fewer pulmonary exacerbations reported in the ivacaftor group compared to placebo (ivacaftor 13 events in 11 patients [n = 34], placebo 17 events in 13 patients [n = 35]). The hazard ratio for time-to-first pulmonary exacerbation was 0.93; p = 0.86.

In the KONTINUE extension study, both the placebo followed by ivacaftor group and the ivacaftor followed by ivacaftor group showed improvement in percent predicted FEV_1 from post-washout baseline to week 12[7]. For both groups combined, the absolute change was 5.15 percentage points (p < 0.0001) (group differences: placebo-ivacaftor, 5.47 percentage points [p = 0.0016]; ivacaftor-ivacaftor, 4.73 percentage points [p = 0.0036])[7,16]. Both the placebo-ivacaftor and ivacaftor-ivacaftor groups showed improvement in CFQ-R[7]; for both groups combined, absolute change from the post-washout baseline at week 12 was 12.27 points (group differences: placebo-ivacaftor, 10.26 points; ivacaftor-ivacaftor, 14.65 points)[7,16]. Sweat chloride was only collected at the baseline and the week two visit; results were consistent with those observed in KONDUCT[7,16].

Table 1. Results of efficacy endpoints in KONDUCT (adults ≥ 18 years) and KONTINUE (adults ≥ 18 years).

	Treatment group	N	Mean	Treatment difference (95% CI): ivacaftor vs placebo	P-value
KONDUCT: change from baseline to week 24					
Absolute change in percent predicted FEV_1 (%)*	Placebo	26	−0.46	4.96 (1.15 to 8.78)	0.0119
	Ivacaftor	24	4.51		
Absolute change in sweat chloride (mmol/l) †	Placebo	26	−4.03	−21.87 (−26.46 to −17.28)	< 0.0001
	Ivacaftor	23	−25.89		
Absolute change in pooled CFQ-R respiratory domain score (points) †¶	Placebo	26	−0.46	12.64 (5.02 to 20.25)	0.0017
	Ivacaftor	24	12.18		
KONTINUE: change from baseline to week 12					
Absolute change in percent predicted FEV_1 (%)*	Placebo-ivacaftor	26	5.47	NA	NA
	Ivacaftor-ivacaftor	20	4.73		
	Both groups combined	46	5.15		
Absolute change in sweat chloride (mmol/l) †§	Placebo-ivacaftor	24	−19.44	NA	NA
	Ivacaftor-ivacaftor	20	−14.75		
	Both groups combined	44	−17.31		
Absolute change in pooled CFQ-R respiratory domain score (points) †¶	Placebo-ivacaftor	26	10.26	NA	NA
	Ivacaftor-ivacaftor	22	14.65		
	Both groups combined	48	12.27		

*Primary endpoint.
†Secondary endpoint.
§Sweat chloride was only collected at baseline and week two.
¶Pooled is defined as all questionnaire versions except for the parent/caregiver version.

CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; FEV_1: predicted forced expiratory volume in one second; NA: not applicable.

3.2 Safety

The main basis for the safety analysis is the 24 week KONDUCT study[1]. Week 12 interim data from the KONTINUE study was also submitted but safety was evaluated by examining serious adverse events (SAEs) only[1]. The Committee for Medicinal Products for Human Use (CHMP) concluded that the safety profile of ivacaftor in patients with *R117H-CFTR* mutation in the KONDUCT and KONTINUE studies was consistent with that observed in previous phase III studies of patients with other mutations of the CF gene[5,7].

In the ≥ 18 year-old age group more patients on placebo than on ivacaftor reported adverse events (AEs): 26 (100%) patients versus 23 (95.8%) respectively[5,7]. AEs more commonly reported by ivacaftor-treated patients (as compared to placebo) were nasal congestion (20.8% vs. 3.8%), oropharyngeal pain (16.7% vs. 0%), and wheezing (16.7% vs. 3.8%)[5,7]. The incidence of infective pulmonary exacerbation of CF was 45.8% (11 patients, 14 events) in the ivacaftor group and 50.0% (13 patients, 23 events) in the placebo group[5,7]. The number of pulmonary exacerbations reported for safety purposes is usually higher than the number of protocol-defined pulmonary exacerbations analysed for efficacy that should meet stricter criteria[5]. The incidence of

cough was 37.5% (nine patients, 12 events) in the ivacaftor group and 26.9% (seven patients, eight events) in the placebo group[5,7]. None of the subjects had haemoptysis[5].

3.3 AWTTC critique

- The KONDUCT study demonstrated that ivacaftor significantly improved lung function, sweat chloride concentrations and CFQ-R respiratory domain scores (above the minimal clinically important difference) in adult patients who have an *R117-CFTR* mutation; improvements were sustained in the interim results of the KONTINUE trial[7].
- Analyses of pre-specified subgroups based on other characteristics associated with baseline disease status showed non-significant trends towards greater response to ivacaftor in groups with more advanced disease or risk of advanced disease such as lower baseline percent predicted FEV_1 or *R117H-5T*[7]*.* CHMP noted the small numbers of patients with an *R117H-7T* genotype and that less evidence of a positive effect of ivacaftor has been shown for patients with an *R117H-7T* mutation associated with less severe disease[5]
- There is currently no licensed medicine available in Wales for patients with the *R117H-CFTR* mutation which targets the underling defect in CF, rather than alleviating symptoms[1].
- There was no significant improvement in BMI with ivacaftor treatment because the majority of the overall population were pancreatic sufficient with a BMI considered to be within a normal range at baseline.
- Due to the low number of patients with pulmonary exacerbations, the company submission states that the analyses cannot infer conclusions regarding the risk of these events[1].
- CHMP highlight that it is not known whether ivacaftor may be efficacious in adult patients with a percent predicted FEV_1 above 90% since only one patient on ivacaftor was available for the analysis[5].
- The author of the KONDUCT study paper noted that the effect size of ivacaftor treatment in this *R117-CFTR* population is smaller than seen in other mutation types such as *G551D* and suggests that intrinsic differences in the molecular defects associated with these mutations might be the cause as *G551D* mutation specifically restricts *CFTR* channel opening (gating), whereas the *R117-CFTR* mutation is multifaceted[7].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] includes a cost-utility analysis (CUA) of oral ivacaftor 150 mg every 12 hours as an adjunct treatment to SoC in patients with CF aged 18 years and older who have an *R117H* mutation in the CF transmembrane conductance regulator (*CFTR*) gene compared to SoC alone which includes daily prophylactic medications and supplements such as pancreatic enzymes, nutritional and vitamin supplements, oral or nebulised antibiotics, nebulised mucolytic agents, steroids, bronchodilators and daily physiotherapy.

An individual-level simulation model with an NHS perspective simulates CF disease progression according to each patient's characteristics and medical history, which are updated every four-weeks for the first two years and annually thereafter. These characteristics feed into a Cox proportional hazards model which is used to adjust the underlying population survival function for each patient in each model cycle to predict survival based on individual percent predicted FEV_1, pulmonary exacerbations, weight-for-age z-score, diabetes status, certain respiratory infections, pancreatic sufficiency, patient age, and gender. Gender, *Staphylococcus (S.) aureus* and *Burkholderia (B.) cepacia* infection status, pancreatic insufficiency, and weight-for-age

z-score were assumed to be constant over time. Gender, age, *S. aureus* and *B. cepacia* infection status, diabetes status and weight-for-age z-score are assumed to be the same in both treatment arms. Ivacaftor is assumed to directly impact percent predicted FEV_1 and to reduce the pulmonary exacerbation rate through increased percent predicted FEV_1[7]. The model also allows for the option of lung transplantation in patients whose FEV_1 drops below 30%, occurrence of adverse events and treatment discontinuation. The model adopts a lifetime horizon to accommodate the entire patient pathway and 3.5% discounting is applied to both costs and benefits.

Most clinical data are taken directly from the KONDUCT trial. Baseline patient characteristics (age, gender, weight-for-age z-score and baseline percent predicted FEV_1) are derived from the baseline characteristics for the 50 adults included in the KONDUCT trial who had percent predicted FEV_1 data available at baseline. Baseline diabetes and infection status are derived from the UK CF registry[17]. Change in percent predicted FEV_1 is taken directly from the KONDUCT trial results for the first 24 weeks. Beyond this point, percent predicted FEV_1 is extrapolated from published sources[18] using US CF registry data of *R117H* patients for SoC and published data[19] from *G551D* patients for ivacaftor. The frequency of pulmonary exacerbations per cycle for patients treated with SoC is calculated using an age-dependent equation relating percent predicted FEV_1 to the annual expected rate of pulmonary exacerbation[20] and a Poisson distribution. For ivacaftor, this rate is multiplied by a rate ratio of 0.446 to reflect the durable treatment benefit observed in previous ivacaftor studies[21]. The proportion of eligible patients who receive a lung transplant is estimated at 24.7% based on UK CF registry data[22]. All patients have a one-time probability of receiving a transplant in the cycle in which percent predicted FEV_1 falls below 30%. Adverse events considered in the model were experienced by at least 15% of ivacaftor patients in the KONDUCT trial with at least 1 percentage point difference between treated and placebo patients and include cough, sputum increased, nasal congestion, oropharyngeal pain and wheezing. The model estimates individual patient risk of death in each cycle using age-specific background mortality hazard derived from UK CF Registry data adjusted for individual patient characteristics that predict survival in CF based on a published Cox proportional hazards model[23]. Post-lung transplantation mortality assumes annual mortality of 15.2% in the first year after transplantation and 6.1% for each subsequent year based on published sources[24].

Cost of treatment is taken from the British National Formulary and adjusted according to the confidential discount price agreed as part of a Wales Patient Access Scheme (WPAS) [commercial in confidence text removed]. A literature review was conducted to identify other healthcare costs (including management costs of exacerbations), costs of adverse events and utility values which were not collected as part of the KONDUCT study. Hospitalisation and other healthcare costs are derived from unpublished evidence for SoC[25]. Hospitalisation costs are assumed to be reduced by 55% for ivacaftor based on the 0.446 rate ratio applied to the pulmonary exacerbation rate and clinical expert opinion reflecting the durable treatment benefit on pulmonary exacerbation rate observed in previous ivacaftor studies. Cost of lung transplantation and follow up are taken from literature[20,26]. Adverse events are costed as a GP visit[27]. The health-related quality of life of CF patients in the model depends on every individual patient's percent predicted FEV_1, history of pulmonary exacerbation and treatment arm. It is based on literature reported utility values, adjusted for a patient's percent predicted FEV_1 and occurrence of pulmonary exacerbation[28] and a utility increment of 0.09 for ivacaftor patients[29]. A utility of 0.810 is assigned to patients after lung transplant[20,26].

Deterministic and probabilistic sensitivity analyses are undertaken to assess parameter uncertainty. Scenario analyses are used to explore the effect of different discontinuation rate and disease management costs as well as alternative data sources and extrapolation techniques on the results.

4.1.2 Results

The results suggest that adjunct treatment with ivacaftor is associated with 13.86 discounted quality-adjusted life-years (QALYs) compared to 9.49 discounted QALYs in the SoC arm at an incremental cost of [commercial in confidence figure removed] (using WPAS price; see Table 2). This gives an incremental cost-effectiveness ratio (ICER) of [commercial in confidence figure removed] per QALY gained. The model projects that ivacaftor leads to an improvement in projected median survival of 7.86 years which is an increase of approximately 18% compared to patients receiving SoC alone. The survival benefit remains across all patient age groups with ivacaftor improving mean residual life years by 66.7% in the 36+ year old group and as much as 87.7% in the 18 to 24 age groups. Overall, the results show the discounted incremental life-years to be 3.29 with an ICER of [commercial in confidence figure removed] per life-year saved. The annual exacerbation rate is suggested to be reduced by 65.0% and the percentage of patients undergoing lung transplantation by 91.0% with adjunctive ivacaftor compared to SoC alone. The time to transplant among those who receive a lung transplant thereby increases by more than 9.3 years.

Table 2. Results of the base case analysis.

	Ivacaftor + SoC	SoC	Difference
Total cost per patient	¶¶	¶¶	¶¶
Drug costs	¶¶	¶¶	¶¶
Hospitalisation costs	£300,579	£344,400	-£43,821
Adverse events costs	£2,251	£762	£1,488
Transplantation costs	£92	£1,696	-£1,605
Total life-years gained per patient	13.98	10.69	3.29
Total QALYs per patient	13.86	9.49	4.37
ICER (£/QALY gained)	¶¶		

¶¶ Commercial in confidence figure removed.

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year; SoC: standard of care.

Table 3 summarises the scenarios provided by the company in order to address uncertainty around the key input parameters. Several scenario analyses were tested using alternative data sources. [Commercial in confidence text removed].

Table 3. Results of the scenario analyses.

Scenarios	ICER	Plausibility
Scenario 1: Alternate base-case incorporating generic pricing at 10% of current net price after 12 years (when patent runs out) and a discount rate of 3.5%.	¶¶	This scenario is plausible as generic pricing after 12 years is realistic and will affect the cost-effectiveness of the treatment.
Scenario 2: Alternative values for percent predicted FEV_1 rate of decline for SoC patients according to Konstan et al, 2012[18].	¶¶	This scenario is less plausible than the base case as the decline rate data is not genotype specific.
Scenario 3: Alternative values for percent predicted FEV_1 rate of decline for SoC patients according to de Boer et al[30].	¶¶	This scenario is less plausible than the base case as the decline rate data is not genotype specific.
Scenario 4: Alternative utility values according to Tappenden et al, 2014[31].	¶¶	This scenario is less plausible than the base case as the utility data is not genotype specific.
Scenario 5: Alternative utility values according to Acaster et al, 2015[32].	¶¶	This scenario is less plausible than the base case as the utility data is not genotype specific.
Scenario 6: Alternative utility values according to Whiting et al, 2014[20].	¶¶	This scenario is implausible. The methodology used to calculate these utilities is unclear and there is little discrimination between highest and lowest $ppFEV_1$ categories.
Scenario 7: No utility increment due to treatment assumed for ivacaftor patients.	¶¶	This scenario is implausible as a utility benefit to patients can be expected based on the improved clinical outcomes.
Scenario 7: Cumulative discontinuation rate of 30% applied for ivacaftor treatment within 15 years of treatment initiation (no further discontinuation beyond that point).	¶¶	This scenario is plausible. It appears reasonable to assume that some patients will discontinue lifelong treatment.
Scenario 8: Gompertz function used to fit survival curves.	¶¶	This scenario is plausible as the Gompertz function was the second best fit for the survival data after the Weibull function used in the base case.
Scenario 9: Alternative adherence of 85% based on observed data for ivacaftor in Wales.	¶¶	This scenario is plausible. It appears reasonable to assume that an adherence rate of 98.9% as observed in the KONDUCT trial will not be realistic for lifelong treatment.

¶¶ Commercial in confidence figure removed.

FEV_1: predicted forced expiratory volume in one second; ICER: incremental cost effectiveness ratio; SoC: standard of care.

The results of the deterministic sensitivity analyses indicate that the ICER is most sensitive to the discount rates, the utility equation and mean absolute change in percent predicted FEV_1 associated with ivacaftor and SoC.

Probabilistic sensitivity analysis suggests that the model results are robust, as the mean results are comparable to the base case results. The probability of ivacaftor to be cost-effective at the willingness to pay thresholds of £20,000 and £30,000 is 0%.

4.1.3 AWTTC critique

The results of the base case CUA indicate that the adjunct use of ivacaftor is considerably more costly but produces increased quality of life and life expectancy compared to SoC alone in CF patients with a *R117H* mutation in the *CFTR* gene resulting in a base case ICER of [commercial in confidence figure removed]. The sensitivity analyses show that the results are sensitive to the discount rates, the utility equation and mean absolute change in percent predicted FEV_1 associated with

ivacaftor and SoC. Scenario analyses using alternative data sources for key parameters suggested ICER values between [commercial in confidence figures removed]. The modelling approach is hampered by the lack of data availability for CF patients with the *R117H* mutation; it is thus uncertain that the company's base case provides a reliable estimate of the ICER value.

Strengths of the economic analysis:

- In the absence of other licensed treatments, SoC appears to be the appropriate comparator for this patient group.
- The model used to calculate cost-effectiveness is well constructed, clearly and logically arranged and appears to be robust and valid.
- The company generally provides a detailed and transparent account of methods and results.
- The company has attempted to validate their model outcomes by comparing survival curves produced by the model to UK CF registry observed curves which produced a good fit.
- The company uses extensive sensitivity analyses to assess the effect of parameter uncertainty on the results.

Limitations of the economic analysis:

- The model appears to assume sustained efficacy of ivacaftor over a patient's lifetime. To date, the only data available for the *R117H* patient population is restricted to 24 weeks. Therefore, there is no longer term data to support this assumption.
- Due to the lack of available data for the *R117H* patient population, various model input data are derived from different patient populations (e.g. *G551D* patients) or the general CF population. This includes the rate of percent predicted FEV_1 decline for *R117H* patients receiving ivacaftor beyond the 24-week KONDUCT period, the rate of pulmonary exacerbations of patients receiving SoC only, healthcare costs, estimates for post-lung transplant mortality and utility values. As these data are not specific to *R117H* patients, any differences in rates, outcomes, costs and quality of life of the *R117H* patient group compared to other genotypes and the general CF population will affect the results to an unknown degree. The model assumes that the specific genotype is known before start of treatment. However, no costs of genetic testing are included in the model which will slightly underestimate overall costs.
- The utility increment of 0.09 for ivacaftor patients is based on unpublished company internal data on file[29] which was not available for review and cannot be verified. It is therefore unclear whether *R117H* patients' quality of life would be adequately reflected in the model.
- The model results suggest a QALY gain of 13.86 over 13.98 life-years in the ivacaftor plus SoC arm. This would suggest a quality of life of 0.99 which is high even for the general population. Considering the impact CF has on patient's lifestyles and the burden of disease, this appears unrealistic. The company suggests that this is common in CF as patients are born with the lifelong condition and do not experience their quality of life as reduced. Therefore, they argue that higher-than-expected values may accurately reflect CF patients' assessments of their own health-related quality of life. Furthermore, they state that these values represent the best available data for CF patients. However, utility values reported in the Solem et al 2016[28] paper appear particularly high with an unrealistic value of 0.949 for percent predicted $FEV_1 > 70$. It is therefore questionable whether the utility values used for the model accurately reflect the quality of life of the patient population.
- Patient characteristics used in the model are derived directly from the KONDUCT study and basing the entire model population on such a small patient number, will introduce bias. The company adjusts for this by using patient-level simulation which will reduce, but not eliminate bias.

- The KONDUCT study was conducted in Europe and the US and although there were sites in Edinburgh and Belfast it is unclear how generalisable the results are to the Welsh patient population.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The UK CF registry data reports that there are an estimated 225 CF adult patients being treated in Wales[6]. Since 11% of CF patients did not complete the review, the number of adults with CF in Wales was adjusted accordingly to 253. Of these patients, 4.61% have an *R117H* mutation in the *CFTR* gene[6]. This equates to approximately 12 adult patients that would be eligible for ivacaftor treatment in year one. Patients become eligible for ivacaftor treatment under the considered license indication when they turn 18 years. It is expected that the cumulative yearly incidence is zero in year two, one in years three and four and two in year five based on the UK CF registry and proportion of patients with a *R117H* mutation. Considering a mortality rate of 1.5%[6], the net number of eligible patients is 12 in year one increasing to 14 in year five. The company assumes 100% uptake and 98.9% adherence[7] due to the lack of alternative treatment options. The annual cost of ivacaftor is [commercial in confidence figures removed] assuming 100% adherence or [commercial in confidence figures removed] assuming 98.9% adherence[33]. Disease management costs and adverse event costs are based on the cost-effectiveness model output.

The company supplied a probabilistic sensitivity analysis that estimates the confidence interval around the five year cumulative budget impact where disease management costs are varied at a standard error of 10% of the mean and patient number estimates from the UK CF registry are varied based on the observed numbers.

5.1.2 Results

The estimated net budget impact as presented by the company is shown in Table 4. The introduction of ivacaftor is estimated to result in additional costs of [commercial in confidence figure removed] in year one increasing to [commercial in confidence figure removed] in year five. The total budget impact over five years would be expected to be in the region of [commercial in confidence figure removed].

Table 4. 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 (CF patients with a *R117H* mutation in the *CFTR* gene)	12	12	13	13	14
Uptake	100%	100%	100%	100%	100%
Treated patients	12	12	13	13	14
Current drug cost (SoC only)	£0	£0	£0	£0	£0
Ivacaftor drug costs*	¶¶	¶¶	¶¶	¶¶	¶¶
Disease management costs (SoC only)	£400,332	£400,332	£433,693	£433,693	£467,054
Disease management costs (ivacaftor)	£245,244	£245,244	£265,681	£265,681	£286,118
Liver function test and adverse event costs (SoC alone)	£852	£852	£923	£923	£994
Liver function test and adverse event costs (ivacaftor)	£1,932	£1,932	£2,093	£2,093	£2,254
Savings from reduced management costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net financial costs	¶¶	¶¶	¶¶	¶¶	¶¶

* [Commercial in confidence text removed]. Drug costs are based on an adherence rate of 98.9%.
¶¶ Commercial in confidence figure removed.

CF: cystic fibrosis; CFTR: CF transmembrane conductance regulator; SoC: standard of care.

Probabilistic sensitivity analysis (PSA) indicates a mean five-year cumulative budget impact of [commercial in confidence figure removed] with a confidence interval between [commercial in confidence figures removed].

5.1.3 AWTTC critique

- The budget impact model provided by the company appears transparent and comprehensive and includes a PSA.
- The company assumes an uptake rate of 100%. Despite the lack of alternative treatment options, it is unclear how realistic this assumption is.
- The company analysis includes mortality and adherence. However, due to the very small patient numbers, mortality is not reflected in the results due to a lack of events. Cost of lung transplantation is not included in the model which will slightly underestimate the total healthcare cost.

5.2 Comparative unit costs

Ivacaftor is a first-in-class medicine for the treatment of CF in patients aged 18 years and older who have an *R117H* mutation 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 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 highlighted ongoing studies that are likely to be available within 6–12 months. End of study results for KONTINUE are currently being finalised and a date for publication is not yet specified.

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: 31 October 2016.
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 the prevalence of the population for the full licensed indication of ivacaftor (Kalydeco®) meets the AWMSG criteria for an ultra-orphan medicine. Using data from the UK CF registry[6], the company extrapolated that 253 adult patients with CF are being treated in Wales of which 4.61% have an *R117H* mutation in the *CFTR* gene. This results in an estimated prevalence of 12 adult patients in Wales who have the *R117H* mutation in the *CFTR* gene and a total of 31 patients for the full licensed indication. Clinical experts in Wales have verified the figures provided by the company.

AWTTC considers ivacaftor (Kalydeco®) to be 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 5) if they consider ivacaftor (Kalydeco®) is an ultra-orphan medicine and the cost per QALY is above the normal thresholds applied.

Table 5. Evidence considered by NMG/AWMSG.

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival.	CF is a rare, life-limiting genetic disease that predominantly causes respiratory disorders (with respiratory failure as the predominant cause of death) but also affects the pancreas, gastrointestinal tract, liver, sweat glands, and reproductive system[34]. Current therapies alleviate symptoms only and require time and effort that imposes a significant burden on patients' and their carers QoL. The *R117H* mutation is associated with variable disease expression ranging from normal to CF[5]. Although the *R117H-CFTR* mutation is associated with progression in lung function decline with age, the severity of CF per age group is generally less than that caused by the *G551D-CFTR* mutation or other *CFTR* mutations associated with a severe phenotype[5].
Whether the medicine addresses an unmet need (e.g. no other licensed medicines).	Ivacaftor is the only treatment which addresses the underlying cause of the disease (the defective *CFTR* protein) in this patient population.
Whether the medicine can reverse or cure, rather than stabilise the condition.	Ivacaftor will not reverse or cure the condition but ivacaftor modifies the course of lung function decline.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy), and that this "definitive" therapy is currently in development.	Ivacaftor does not bridge a gap to definitive therapy. The company note that gene therapy is being explored through clinical trials.
The innovative nature of the medicine.	Ivacaftor is the first medicine that addresses the underlying cause of CF with the potential to reduce disease progression and increase survival in patients aged 18 years and older who have an *R117H* mutation in the *CFTR* gene. Ivacaftor is a *CFTR* potentiator, enhancing the channel open probability of the *CFTR* protein at the cell surface.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on QoL 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 company suggests that, as patients are born with the disease and perceive their reduced QoL as 'normal', generic QoL measures such as the EQ-5D do not adequately reflect the impact of the disease on patients' QoL. Furthermore, it is challenging to measure improvements in health-related QoL scores. Declining lung function and breathlessness impact patients QoL and ability to work or study. CF thus imposes a significant societal and economic burden. In a study of 254 patients with CF in the UK, 40% of patients reported that they had stopped work due to CF[35]. An improvement in lung function 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).	The time spent caring for patients with CF has a negative impact on daily activities, family life, social activities and work productivity. In addition, mental health problems, including anxiety and depression are frequently reported in both CF patients and caregivers[36]. The company suggests that benefits of ivacaftor treatment are likely to lead to improved health, delay in disease progression and increased survival for patients with CF. These benefits will translate into an improvement in the general health of caregivers.
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; BMI: body mass index; CF: Cystic Fibrosis; *CFTR*: CF transmembrane conductance regulator; NMG: New Medicines Group; QALY: quality-adjusted life-year; QoL: quality of life; SoC: standard of care.	

GLOSSARY

CFQ-R
The cystic fibrosis questionnaire-revised (CFQ-R) is a disease-specific, patient-reported outcome measure of health-related quality of life[37].

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[38].

Percent of predicted FEV_1
FEV_1 expressed as a percentage of a predicted value, calculated using a reference population[39].

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