

7.12 IVACAFTOR tablet, 150mg, Kalydeco®, Vertex Pharmaceuticals

1 Purpose of Item

- 1.1 This minor submission provided additional efficacy and safety data on the use of ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older with a G551D or other gating (class III) mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene who have severe CF disease (forced expiratory volume in one second (FEV₁) <40% predicted), as requested by the PBAC. The submission stated that the clinical evidence presented [REDACTED].
- 1.2 While considering previous ivacaftor submissions, the PBAC noted that “limited evidence is available for ivacaftor in more severe patients; i.e. those with a predicted FEV₁% of less than 40%” (p2, ivacaftor public summary document (PSD), November 2013 PBAC meeting). The populations of the key trials in previous submissions, STRIVE (G551D mutation), ENVISION (G551D mutation) and KONNECTION (non-G551D gating mutation), were restricted to patients with a FEV₁ ≥40% predicted at screening.

2 Requested listing

- 2.1 The submission did not seek a new listing for ivacaftor.

3 Background

- 3.1 Ivacaftor was listed on the Australian Register of Therapeutic Goods (ARTG) on 14th August 2014 for the treatment of CF in patients age 6 years and older who have a G551D or other gating (class III) mutation in the CFTR gene. Before this date, ivacaftor was registered with the Therapeutic Goods Administration (TGA) for the treatment of CF in patients age 6 years and older who have a G551D mutation in the CFTR gene.
- 3.2 At the July 2013 meeting, the PBAC considered a major submission for ivacaftor which sought a listing for treatment of CF patients aged 6 years and older who have a G551D mutation in the CFTR gene. The PBAC noted that it might be possible to reduce the dose of ivacaftor in clinical practice by co-administering ivacaftor with a strong CYP3A inhibitor. But even with a dose reduction, the cost per quality-adjusted life-year (QALY) would remain too high. The PBAC decided to defer making a recommendation to allow the sponsor to consider the Committee’s views and to submit a new price proposal for PBS listing (Ivacaftor PSD, July 2013 PBAC meeting).
- 3.3 A minor submission was considered at the November 2013 meeting. The PBAC considered the sponsor’s arguments and concluded that the current data about the

dose of ivacaftor when used with other CYP3A4 inhibitors (e.g. macrolide antibiotics) was limited and would therefore not support, at this point in time, a PBS restriction in which a subsidy would only be provided for ivacaftor if used with a booster-like regimen. The PBAC recommended the listing of ivacaftor for treatment of CF patients aged 6 years or older who have a G551D mutation. The PBAC expressed the view that ivacaftor would not be cost-effective under the sponsor's pricing proposal. The PBAC considered that the cost-effectiveness of ivacaftor would be acceptable if the incremental cost-effectiveness ratio (ICER) was between \$60,000-80,000 per QALY gained, and if risk sharing agreements were implemented, including a "pay-for-performance" arrangement whereby the sponsor would provide funding for the supply of ivacaftor for patients without objective clinical response (see below for details). The PBAC further considered that the risk-sharing agreement with the sponsor should commit the sponsor to providing ongoing funding for collection of data in all patients receiving PBS funded ivacaftor, addressing a number of areas outlined in detail in the PSD. The PBAC requested that this information be presented for analysis after 12 and 24 months of data are available (Ivacaftor PSD, November 2013 PBAC meeting).

3.4 At the March 2014 meeting, the PBAC considered a major submission for ivacaftor which requested an extension of the PBS restriction to include patients with any Class III gating mutation of the CFTR gene. The PBAC noted at the time that the indication for other Class III gating mutations was being progressed under the TGA-PBAC parallel process. The PBAC decided that, as a positive TGA Delegate's Overview for other Class III gating mutations was not available at the time of consideration in March 2014, the restriction should specify only patients with a G551D mutation. Once the sponsor was able to make a resubmission with the TGA documentation for other Class III gating mutations, the PBAC indicated that it would consider amending the restriction to include those patients at that time. The PBAC reiterated the view that the cost-effectiveness of ivacaftor would be acceptable if the ICER would be around \$60,000-\$80,000 per QALY and if a "pay for performance" arrangement of the nature described below were implemented, together with the other risk sharing measures also identified below:

- An agreement between the sponsor of ivacaftor and the Government to cap the maximum financial expenditure to the submission's estimates with a 100% rebate thereafter;
- A "pay-for-performance" arrangement whereby the sponsor rebates to the Commonwealth 100% of the cost of treatment with ivacaftor received by patients who are subsequently assessed as not responding to treatment every 3 and 6 months. Response for that purpose should be defined as at least a 5% improvement in FEV₁ from baseline after 3 months' treatment, and at least 10% improvement from baseline after 6 months' treatment. For patients aged 6 to 11 years that are able to show improvement in FEV₁ but less than the threshold for PBS subsidy, the assessment of clinical response may also include a weight gain of 1.5kg at 3 months and/or 3kg at 6 months;
- Where a patient currently uses a moderate or strong CYP3A inhibitor known to influence the pharmacokinetics of ivacaftor which must trigger a dose adjustment as per the recommended dose in the Product Information (PI) (150mg once daily for moderate inhibitors, 150mg twice weekly for strong inhibitors), the subsidy only be paid for the adjusted dose, with any difference between what is being used in clinical practice versus recommended PI dose to be rebated by the sponsor;

- Commitment by the sponsor for ongoing funding for collection of data in all patients receiving PBS-funded ivacaftor in accordance with the views expressed by the PBAC in November 2013; and
- Every 12 months of data to be provided to the PBAC for assessment and comparison between the clinical trial and assumptions in the economic analysis and real life clinical experience (Ivacaftor PSD, March 2014 PBAC meeting).

3.5 At the November 2014 meeting, the PBAC recommended to extend the previous recommendation for the PBS listing of ivacaftor as a Section 100 (Highly Specialised Drugs Program) benefit for the treatment of CF in patients aged 6 years and older who have a G551D mutation in the CFTR gene to include other gating (class III) mutation in the CFTR gene (Ivacaftor PSD, November 2014 PBAC meeting).

4 Clinical place for the proposed therapy

4.1 Ivacaftor is used as an add-on to current best supportive therapy and has a different mechanism of action to the antibiotics and mucolytics currently available through the PBS for treatment of patients with CF. CF is an autosomal recessive disease caused by mutations in the CFTR gene. The encoded protein, CFTR, is an epithelial chloride ion channel responsible for the regulation of salt and water absorption and secretion in multiple organ systems. Ivacaftor is a novel selective CFTR potentiator, which improves the function of the CFTR protein.

5 Comparator

5.1 The PBAC has previously accepted best supportive care as the appropriate comparator (ivacaftor PSD, November 2013 PBAC meeting). Best supportive care consists of usual respiratory, nutritional and rehabilitative support (e.g. mucolytics, osmotic agents, antibiotics, bronchodilatation, pancreatic enzymes, dietetic therapy, and chest physiotherapy).

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The clinical evidence presented in the submission was based on data from:

- Severe CF patients with a G551D mutation who were involved in Compassionate Access Programs (CAPs) in Australia, UK/Ireland, Germany, France and the US;

- Subgroups of G551D CF patients from a randomised placebo-controlled trial (STRIVE) and from an open-label extension study of two randomised controlled trials (STRIVE and ENVISION), namely PERSIST, who had a FEV₁<40% predicted at treatment initiation or at the time of rollover and were treated with ivacaftor¹; and
- Patients in the US CF Foundation Patient Registry (CFFPR) who received CF treatment with ivacaftor.

Table 1: Studies and associated reports presented in the minor submission

Study	Protocol title / Publication title	Publication citation
CAP in Australia (Wainwright 2014)	Wainwright C., Bell S. Morton J., <i>et al.</i> The effect of ivacaftor in individuals with cystic fibrosis and severe lung disease: analysis of data from the Australian Named Patient Program. (Abstract)	Annual Scientific Meeting of the Thoracic Society of Australia and New Zealand and the Australian and New Zealand Society of Respiratory Science, Adelaide, Australia, 4-9 April 2014
CAP in UK/Ireland (Barry 2010)	Barry P.J., Plant B.J., Nair A., <i>et al.</i> Effects of Ivacaftor in cystic fibrosis patients carrying the G551D mutation with severe lung disease.	<i>Chest</i> 2010; 146(1): 152-8.
CAPs in Germany (Hebestreit 2013)	Hebestreit H., Sauer-Heiborn A., Fischer R., <i>et al.</i> Effects of ivacaftor on severely ill patients with cystic fibrosis carrying a G551D mutation	<i>Journal of Cystic Fibrosis</i> 2013; 12: 599-603
CAP in France (ATU study)	ATU Cohort Periodic Report. Temporary authorisation of use (ATU) periodic cohort report: Periodic safety and efficacy report of the use of VX-770 (ivacaftor 150mg) in the French ATU cohort. Reporting period: 21 July 2012 – 12 October 2012	November, 2012
CAP in US (Taylor-Cousar 2015)	Taylor-Cousar J., Niknian M., Gilmartin G., <i>et al.</i> Effect of ivacaftor in patients with advanced cystic fibrosis and a G551D-CFTR mutation: Safety and efficacy in an expanded access program in the United States.	<i>Journal of Cystic fibrosis</i> 2015 [In press]
Severe disease subgroups in STRIVE and PERSIST (Bell 2013)	Bell S., Rodriguez S. and Lubarsky B. Effect of ivacaftor in patients with cystic fibrosis and the G551D-CFTR mutation who have severe lung dysfunction or lung function in the normal range. (Abstract)	The 10 th Australasian Cystic Fibrosis Conference, Auckland, New Zealand, 17-20 August 2013
US CFFPR (Bai 2015)	Bai Y., Higgins M., Volkova N., <i>et al.</i> Ivacaftor long-term safety study: analysis of 2013 US CF Foundation patient registry data (Abstract)	North American Cystic Fibrosis Conference, Phoenix, US, October 2015 (under embargo)

CAP = Compassionate Access Program; CF = cystic fibrosis; CFFPR = Cystic Fibrosis Foundation Patient Registry; CFTR = cystic fibrosis transmembrane conductance regulator

Source: Table compiled for the purpose of the Overview

6.4 The key features of the clinical studies are summarised in Table 2.

¹ The subgroup analysis of PERSIST only included patients randomised to receive placebo during the prior controlled trials whose FEV₁ was <40% of predicted upon rollover to open-label treatment with ivacaftor; whereas the STRIVE subgroup analysis included patients randomised to both treatment arms (ivacaftor and placebo) who had baseline FEV₁ <40% at treatment initiation.

Table 2: Key features of the clinical evidence

Study	N	Design	Follow-up duration	Patient population	Outcome																																										
CAP in Australia (Wainwright 2014)	17 (ivacaftor)	Retrospective, open-label, comparative study	Unknown ^a	Patients with severe CF who had a G551D mutation	<ul style="list-style-type: none"> ● Change in FEV₁ from baseline ● Change in body weight ● Number of hospital admissions ● Length of hospital stay 																																										
	314 (control)			Patients from ACFNDR who had moderate or severe disease and did not carry G551D mutation		CAP in UK/Ireland (Barry 2014)	21 (ivacaftor)	Retrospective, open-label, comparative study	7.8 months	CF patients with the presence of at least one G551D allele who had severe disease and/or were on the lung transplant waiting list	<ul style="list-style-type: none"> ● Change in FEV₁ from baseline ● Change in body weight ● Length of treatment with IV antibiotics ● Incidence of AEs 	35 (control)	Non-G551D CF patients who had severe disease and/or were on the lung transplant waiting list	CAP in Germany (Hebestreit 2013)	14	Retrospective, open-label, non-comparative study	7.7 months	Patients with severe CF who carried a G551D mutation	<ul style="list-style-type: none"> ● Change in FEV₁ from baseline ● Change in body weight ● Incidence of AEs 	CAP in France (ATU study)	8	Open-label, non-comparative study	12 weeks	CF patients with severe disease who had the G551D mutation in at least 1 allele	<ul style="list-style-type: none"> ● Change in FEV₁ from baseline ● Change in body weight 	CAP in US (Taylor-Cousar 2015)	44	Prospective, open-label, non-comparative study	24 weeks	Patients with severe CF and with a G551D mutation	<ul style="list-style-type: none"> ● Incidence of AEs ● Change in FEV₁ from baseline ● Change in body weight 	STRIVE subgroup (Bell 2013)	5 (ivacaftor)	Prospective, blinded, comparative study	48 weeks	Patients with severe CF who had a G551D mutation	<ul style="list-style-type: none"> ● Change in FEV₁ from baseline ● Change in body weight ● Change in sweat chloride level 	8 (control)	PERSIST subgroup (Bell 2013)	8 (ivacaftor)	Prospective, open-label, non-comparative study	48 weeks	Patients with severe CF who had the G551D CFTR mutation in at least 1 allele	<ul style="list-style-type: none"> ● Change in FEV₁ from baseline ● Change in body weight 	US CFFPR (Bai 2015)	999 (control)	Open-label, comparative study
CAP in UK/Ireland (Barry 2014)	21 (ivacaftor)	Retrospective, open-label, comparative study	7.8 months	CF patients with the presence of at least one G551D allele who had severe disease and/or were on the lung transplant waiting list	<ul style="list-style-type: none"> ● Change in FEV₁ from baseline ● Change in body weight ● Length of treatment with IV antibiotics ● Incidence of AEs 																																										
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ACFNDR = Australian Cystic Fibrosis National Data Registry; AE = adverse event; CAP = Compassionate Access Program; CF = cystic fibrosis; CFFPR = Cystic Fibrosis Foundation Patient Registry; CFTR = cystic fibrosis transmembrane conductance regulator; FEV₁ = forced expiratory volume in one second; IV = intravenous

^a The study included 17 patients who were granted access for treatment with ivacaftor between April 2012 and July 2013. The follow-up period of these patients, however, was not reported.

Source: Table compiled for the purpose of the Overview, based on study information from published papers, conference abstracts or study report on the included studies

6.5 The study populations were restricted to patients with severe CF and with a G551D CFTR mutation in all studies except the US CFFPR, for which the information on disease severity and CFTR genotype was not provided. Clinical data presented in the submission related to a total of 114 severe CF patients with G551D mutation in the CFTR gene on at least 1 allele, which accounts for approximately 38% of the worldwide population as estimated by the submission (N=300).

- 6.6 The submission did not provide any evidence indicating the effectiveness and safety of ivacaftor in patients with severe CF who have a non-G551D class III mutation. The March 2014 major submission assumed that there were approximately 10 patients in Australia who possess class III (gating) mutations other than G551D, based on the Australian Cystic Fibrosis Data Registry (ACFDR) Annual Report² and correspondence with the ACFDR (Ivacaftor PSD, November 2014 PBAC meeting). Given the ACFDR's estimate of 9.4% Australian CF patients with severe lung function impairment and assuming a similar distribution of disease severity across CFTR genotypes, there would only be about one patient in Australia who has severe CF with a non-G551D gating mutation.
- 6.7 A 'no treatment' control group was included in the following four studies:
- Australia CAP: data from the ACFDR were obtained for patients who were pancreatic insufficient³, carried no G551D mutation and who had a starting FEV₁ in either the "severe" or "moderate" categories, effectively <70% predicted;
 - UK/Ireland CAP: patients receiving ivacaftor via the CAP were matched for gender and age (+/- 5 years). Control patients were also required to meeting the inclusion criteria for the CAP⁴ with the exception of genotype;
 - STRIVE subgroup: the control group included CF patients with the G551D mutation randomised to receive placebo who had FEV₁ of 40% to 90% at screening (one trial eligible criterion) but had baseline FEV₁ of <40% at randomisation (due to within-patient fluctuations in FEV₁);
 - US CFFPR: patients treated with ivacaftor were matched with patients who never received ivacaftor on age, gender and CFTR genotype.

In comparison with subjects receiving ivacaftor via CAPs, control patients had less severe disease in the Australian study (FEV₁ <70% predicted vs FEV₁ <40% predicted) and had different CFTR mutations in the Australian and UK/Ireland studies (G551D mutation vs non-G551D mutation).

Comparative effectiveness

- 6.8 Table 3 summarises the main results from the included studies in terms of change from baseline in % predicted FEV₁.

² ACFDR Annual Reports are available at: <http://www.cysticfibrosis.org.au/cfa/data-registry>

³ Pancreatic insufficiency is the most common gastrointestinal complication of CF, affecting approximately 85% of patients at some time in their lives. Absence or dysfunction of CFTR in pancreatic duct cells results in exocrine pancreatic insufficiency and consequential malnutrition.

⁴ Inclusion criteria: 1) the presence of at least one G551D allele; and 2) highest FEV₁ <40% predicted in the preceding 6 months and/or on the lung transplant listing

Table 3: Results of change from baseline in FEV₁ % predicted

Study	Treatment group	N	FEV ₁ % predicted, mean (SD)		Absolute change in FEV ₁ % predicted		Between group comparison, p-value
			Baseline ^a	Post-treatment ^a	Mean (SD)	p-value	
CAP in Australia (Wainwright 2014)	Ivacaftor	17	38.3 (12.4)	48.6 (17.8)	10.3 (8.1)	<0.001	<0.001
	Control	314	45.4 (14.5)	45.1 (13.7)	-0.4 (9.1)	NS	
CAP in UK/Ireland (Barry 2014)	Ivacaftor	21	26.5 (7.2)	30.7 (9.9)	4.2	0.007	0.003
	Control	35	30.3 (7.5)	NR	0.6 (-2.1, 2.8) ^b	NR	
CAP in Germany (Hebestreit 2013)	Ivacaftor	14	25.0 (7.5)	NR	5.2 (5.6)	0.005	–
CAP in France (ATU study)	Ivacaftor	8 ^c	31.2 (7.1) ^c	35.2 (5.7) ^c	4.1 (5.2)	NS	–
CAP in US (Taylor-Cousar 2015)	Ivacaftor	44 ^d	29.6 (6.3) ^d	NR	5.5 (5.3) ^d	NR	–
STRIVE subgroup (Bell 2013)	Ivacaftor	5 ^e	38.2 (0.9)	NR	7.9 (7.6) ^e	NR	NS ^f
	Control	8	35.9 (2.6)	NR	1.9 (7.0)	NR	
PERSIST subgroup (Bell 2013)	Ivacaftor	8 ^g	34.5 (3.7)	NR	14.5 (9.0) ^g	NR	–

CAP = Compassionate Access Program; FEV₁ = forced expiratory volume in one second; NR = not reported; NS = non-significant; SD = standard deviation

^a Data on FEV₁ % predicted values at baseline and post-treatment were obtained from published papers, conference abstracts or study report on the included studies.

^b Results were presented as median (interquartile range)

^c Three (out of 8) patients with missing data on FEV₁ % at Week 12 were excluded from analysis.

^d FEV₁ reported for spirometry subset: includes only patients with baseline spirometry assessed ≤31 days prior to first dose of study treatment. n=35 at baseline and n=19 at Week 24.

^e One (out of 5) patient discontinued or had data unavailable and was not included in the analysis.

^f Using unpaired *t* test.

^g Six (out of 8) patients discontinued or had data unavailable and were not included for assessment

Source: Table 5, p15 of the minor submission

- 6.9 Results of changes in FEV₁ % predicted from baseline indicated that patients receiving ivacaftor for treatment of severe CF with the G551D CFTR mutation experienced an improvement in lung function during follow-up periods of 3 to 11 months across studies. In the three comparative studies, increases in FEV₁ % predicted were consistently higher in the ivacaftor groups than in the control groups (3.8%-7.9% vs -0.4%-1.9%), although the differences between the two treatment groups were not always statistically significant.
- 6.10 The PBAC has previously accepted that “the demonstrated 10% improvement in FEV₁ over a period of up to 2 years is clinically significant and important” (p12, Ivacaftor PSD, November 2013 PBAC meeting). A mean absolute increase in FEV₁ % predicted of >10% from baseline was only reported in the PERSIST subgroup (14.5%±9.0%) and the Australian CAP (10.3%±8.1); the former study had a 75% attrition rate (6 out of 8), with only two patients included in the Week 48 assessment, while the latter study had a mean baseline % predicted FEV₁ close to 40% (38.3%). In patients with more severe disease at baseline, a smaller improvement of lung function was observed (change of 3.8%-5.5% in FEV₁ % predicted in CAPs in UK/Ireland, Germany, France and UK).
- 6.11 The submission acknowledged that the absolute changes in FEV₁ % predicted for most patients with severe lung dysfunction were not as large as those observed in the key trials included in previous submissions, where patients with mild or moderate disease at screening were enrolled (change at Week 48 in STRIVE and ENVISION:

10.0%-10.5%; Ivacaftor PSD, November 2014). The submission argued that improvement in FEV₁ should be considered in the context of the degree of lung impairment of these patients prior to ivacaftor treatment, as it is known to be more difficult to show large absolute changes in FEV₁ % predicted in patients with poor lung function at baseline (Tobramycin PSD, March 2011 PBAC meeting). However, the submission did not provide evidence to demonstrate that a smaller absolute change in FEV₁ % predicted in patients with severe CF is clinically important, e.g. associated with reduced mortality.

6.12 Table 4 summarises the results of change in body weight across clinical studies.

Table 4: Results of change in body weight

Study	Treatment group	N	Body weight, mean (SD), kg		Absolute change in body weight, kg		Between group comparison, p-value
			Baseline ^a	Post-treatment ^a	Mean (SD)	p-value	
CAP in Australia (Wainwright 2014)	Ivacaftor	17	57.7 (12.2)	60.5 (12.4)	2.8 (5.0)	0.036	0.02
	Control	314	57.7 (11.4)	58.5 (11.4)	0.8 (3.3)	<0.001	
CAP in UK/Ireland (Barry 2014)	Ivacaftor	21	49.8 (44.4, 60.7) ^b	51.6 (48.6-66.8) ^b	2.3 (-0.4, 4.2) ^b	0.006	0.25
	Control	35	54.0 (49.0, 62.4) ^b	NR	0.6 (-0.5, 3.2) ^b	NR	
CAP in Germany (Hebestreit 2013)	Ivacaftor	14	56 (10)	NR	2.1 (2.4)	0.005	–
CAP in France (ATU study)	Ivacaftor	8 ^c	60.8 (8.3) ^c	62.9 (8.6) ^c	2.1 (2.0) ^c	NS	–
CAP in US (Taylor-Cousar 2015)	Ivacaftor	44 ^d	58.9 (15.4)	NR	3.3 (4.0) ^d	NR	–
STRIVE subgroup (Bell 2013)	Ivacaftor	5 ^e	61.0 (5.4)	NR	1.4 (2.6) ^e	NR	NS ^f
	Control	8	55.1 (11.6)	NR	-0.2 (3.0)	NR	
PERSIST subgroup (Bell 2013)	Ivacaftor	8 ^g	63.4 (23.0)	NR	3.5 (4.2) ^g	NR	–

CAP = Compassionate Access Program; NR = not reported; NS = non-significant; SD = standard deviation

^a Data on body weight at baseline and post-treatment were obtained from published papers, conference abstracts or study report on the included studies.

^b Results were presented as median (interquartile range)

^c Three (out of 8) patients were excluded from analysis due to lack of Week 12 data.

^d Change in body weight at Week 24 were reported in 25 (out of 44) patients

^e One (out of 5) patient discontinued or had data unavailable and was not included in the analysis

^f Using unpaired *t* test.

^g Six (out of 8) patients discontinued or had data unavailable and were not included in the analysis

Source: Table 5, p15 of the minor submission

6.13 During follow-up periods of 3 to 11 months, the mean body weight of patients who received ivacaftor to treat severe CF increased by 1.4kg to 3.5kg across studies, comparable to the results from key trials relating to patients with less severe disease – change at Week 48 in STRIVE and ENVISION: 2.7-2.8kg; Ivacaftor PSD, November 2014). A statistically significantly greater weight gain in patients receiving ivacaftor than in the controls was reported by the CAP in Australia (p=0.02).

6.14 Data from the Australian and UK/Ireland CAPs showed that ivacaftor was associated with substantial decreases (pre-treatment vs post-treatment) in the median number of hospital admissions per year (4.0 vs 0.6, p<0.001) and the median length of hospital stay (46 days vs 2.9 days, p=0.009), the median number of inpatient intravenous (IV) antibiotic days (23 days per year vs 0 day per year, p=0.001) and the median total IV

days (74 days vs 38 days, $p=0.002$). Improvement in hospitalisation and IV antibiotic requirements in patients receiving ivacaftor were also significant compared to control subjects. The incidence of pulmonary exacerbation in severe CF patients receiving ivacaftor was reported in the US CAP as an adverse event (AE). During a 24-week treatment period, 39 pulmonary exacerbation events were reported in 20 (45%) patients. Of these events, 22 required IV antibiotics and 17 required hospitalisations. Pulmonary exacerbation was considered the cause of death in three patients (6.8%). Data on the pre-treatment incidence of pulmonary exacerbation were not available for comparison.

- 6.15 Results of change in sweat chloride concentration were only reported for the severe disease subgroup of patients in the STRIVE trial. Following treatment with ivacaftor, the mean sweat chloride concentration decreased from baseline by 35.7 ± 37.5 mmol/L at Week 48 (baseline: 98.2 ± 11.6 mmol/L); whereas for patients in the placebo arm, the mean sweat chloride level at Week 48 was similar to the baseline value (mean change: -0.1 ± 11.0 mmol/L). The change in sweat chloride concentration reported in the ivacaftor-treated patients in STRIVE met the definition of treatment response in a clinical commissioning policy on ivacaftor treatment produced by the UK's National Health Service⁵, i.e. a sweat chloride level below 60 mmol/L or 30% less than baseline.
- 6.16 In the 5-year observational study of the US CFFPR, the average duration of ivacaftor exposure was 1.4 years among the treated CF patients. In 2013, the annual risks of death, organ transplantation, hospitalisation and pulmonary exacerbation were all statistically significantly lower in the ivacaftor cohort than in the matched comparator cohort (Table 5). Trends were similar when analyses were stratified by age and % predicted FEV₁.

Table 5: Summary of key outcomes in the US CFFPR, 2013

Outcome	Ivacaftor (N=999)		Comparator (n=4,932)		Relative risk [95% CI]
	n	Risk (%)	n	Risk (%)	
Death	5	0.5	66	1.3	0.37 [0.15, 0.93]
Organ transplantation	2	0.2	53	1.1	0.19 [0.05, 0.76]
Hospitalisation	247	24.7	2,055	41.7	0.59 [0.53, 0.66]
Pulmonary exacerbation	256	25.6	2,037	41.3	0.62 [0.56, 0.69]

CI = confidence interval; CFFPR = Cystic Fibrosis Foundation Patient Registry

Source: Table 4, p19 of the submission

- 6.17 The submission noted several limitations of the included studies:
- The retrospective data collection or post hoc analysis in most of the studies. Patients who discontinued treatment or had missing data were not included for analysis in the CAPs in France ($n=3$ (38%) at Week 12) and the US ($n=25$ (57%), $n=19$ (43%) for FEV₁ and weight, respectively, at Week 24) and in the subgroup analyses of STRIVE ($n=1$ (20%) at Week 48) and PERSIST ($n=6$ (75%) at Week 48). It is unknown whether this occurred in other studies as well. If patients withdrew from ivacaftor therapy or were lost to follow-up due to lack of treatment response or disease exacerbation, the efficacy results would have been biased in favour of ivacaftor;

⁵ Available at: www.england.nhs.uk/wp-content/uploads/2013/04/a01-p-b.pdf

- The lack of a randomised placebo arm. Although ‘no treatment’ groups were included in three studies, due to the non-randomised design of the studies, patients in the two treatment arms were not comparable in terms of baseline lung function, CFTR genotype and/or other patient characteristics that would be expected to affect prognosis; and
- The small number of severe CF patients in each study. The average responses reported in these studies were susceptible to outliers.

Furthermore, ivacaftor is intended to be used in addition to best supportive care. Information on background therapies in the included studies was not provided. It is unclear whether the observed improvements in health outcomes following ivacaftor treatment, or differences between the ivacaftor and control groups, were entirely attributable to the use of ivacaftor, or due to a combination of ivacaftor and differences in concomitant therapies used to manage CF.

Comparative harms

- 6.18 The submission did not present any comparative safety data for ivacaftor + best supportive care versus best supportive care alone.
- 6.19 Safety data were reported for three studies. In the UK/Ireland CAP, no AEs were considered by the clinicians to be secondary to ivacaftor. In the CAP in Germany, three (21.4%) patients experienced more secretions both in the bronchi and nasal cavity. One patient reported to “suffocate” from the secretions so that IV antibiotic therapy was initiated and the ivacaftor therapy was discontinued. No additional severe AEs were reported in this study. During the course of the US CAP, AEs were reported in 38 (86.4%) patients. The most frequently reported AEs, e.g. pulmonary exacerbation (19 patients, 43.2%), were consistent with those that would be expected in patients with advanced CF lung disease. Serious AEs were reported in 14 (31.8%) patients, including pulmonary exacerbation, pneumothorax, upper respiratory tract infection, haemoptysis, gastroenteritis, acute respiratory failure, secondary adrenocortical insufficiency, syncope, abdominal pain, and abnormal liver test. Pulmonary exacerbation was the most common serious AE (10 patients, 22.7%). AEs resulted in treatment withdrawal in two patients: one due to severe abdominal pain; the other due to dizziness and tinnitus. Three (6.8%) deaths were reported in the US CAP. All were the result of pulmonary exacerbations and considered unrelated to study drug by the clinician.

Clinical claim

- 6.20 The submission claimed that the treatment benefits of ivacaftor in CF patients aged 6 years and older with at least one copy of the G551D mutation, as reported in the key trials relating to patients with mild or moderate CF (STRIVE, ENVISION and KONNECTION), are applicable to patients with severe disease ($FEV_1 < 40\%$ predicted). The average magnitude of the improvement in lung function in patients with severe CF, as measured by change in FEV_1 % predicted, in most studies was smaller than that observed in patients with less severe disease and did not reach the clinically important difference previously accepted by the PBAC. Clinical data showed that the use of ivacaftor in CF patients with severe lung function impairment was associated with weight gain, less hospitalisation and fewer IV antibiotic requirements. Interpretation of these results should take into consideration the potential for confounding due to differences in background CF management, the lack of

comparable placebo control group, the high loss to follow-up and the small sample size of the clinical studies.

- 6.21 The submission indicated that the significant reductions in risks of death and lung transplantation, as reported in the US CFFPR study, are a potential early indicator of disease modification by CFTR modulatory therapy. While considering the clinical evidence presented in the November 2013 submission, the PBAC expressed concerns regarding whether the short-term result of change in % predicted FEV₁ would translate into long-term survival benefits, and the lack of long-term safety data on ivacaftor (Ivacaftor PSD, November 2013). Given that ivacaftor therapy is likely to be life-long and the absence of long-term survival and safety data, these remain as major issues to be addressed.
- 6.22 The PBAC considered that the clinical evidence presented in the submission showed some benefit in severe CF group however, the PBAC noted that the absolute increase in FEV₁ was lower in patients under the compassionate access program across different countries than observed among patients in the PERSIST trial (refer Table 3 above). The PBAC considered that it remains uncertain whether this will translate into significant patient relevant improvements in health.

Economic analysis

- 6.23 There was no economic comparison presented.

Estimated PBS usage & financial implications

- 6.24 Estimated financial implications were not presented in the minor submission.

For more detail on PBAC's view, see section 7 "PBAC outcome".

7 PBAC Outcome

- 7.1 The PBAC recommended to continue the subsidy of ivacaftor as a Section 100 (Highly Specialised Drugs Program) benefit for the treatment of cystic fibrosis (CF) in patients aged 6 years and older with a G551D or other gating (class III) mutation in cystic fibrosis transmembrane conductance regulator (CFTR) gene who have severe CF disease (forced expiratory volume in one second (FEV₁) <40% predicted).
- 7.2 The PBAC noted the additional efficacy and safety data on the use of ivacaftor for the severe CF. The PBAC considered that the clinical evidence presented in the submission showed some benefit in severe CF group however, the PBAC noted that the absolute increase in FEV₁ was lower in patients under the compassionate access program across different countries than observed among patients in the PERSIST trial (refer Table 3 above). The PBAC considered that it remains uncertain whether this will translate into significant patient relevant improvements in health.
- 7.3 The PBAC emphasised that this recommendation was in the context of a patient group with severe CF who did demonstrate a benefit with ivacaftor, albeit a smaller absolute improvement in FEV₁ than observed in the original positive recommendation for ivacaftor in March 2014. The PBAC considered that this recommendation would

not represent a precedent for accepting less than 10% FEV₁ improvement in future submissions.

- 7.4 The PBAC noted the submission did not provide any evidence indicating the effectiveness and safety of ivacaftor in patients with severe CF who have a non-G551D class III mutation. The PBAC noted there may be about one patient in Australia who has severe CF with a non-G551D class III mutation.
- 7.5 Notwithstanding the concerns stated above, the PBAC considered that it may be reasonable to [REDACTED] patients who have severe CF disease FEV₁ <40% (predicted). The PBAC agreed that the severe CF patient group will be limited to the G551D and other (gating class III) mutation groups only, and will not apply to other mutations of CFTR gene (e.g F508del).
- 7.6 The PBAC noted that under the compassionate access program in Australia there are [REDACTED] patients with severe CF that may be eligible for treatment with ivacaftor.
- 7.7 The PBAC noted that the severe CF disease group would need to meet the eligibility and continuation criteria as had been previously recommended [REDACTED].
- 7.8 The PBAC also noted [REDACTED].

Outcome:

Recommended

8 Recommended listing

- 8.1 No change to the existing listing

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.