

## 6.11 IVACAFTOR

Tablet; 150 mg;

Kalydeco<sup>®</sup>; Vertex Pharmaceuticals (Australia) Pty Ltd.

### 1 Purpose of Application

- 1.1 The minor submission requested an extension of the PBAC's previous recommendation for the PBS listing of ivacaftor as a Section 100 (Highly Specialised Drugs Program) benefit for the treatment of cystic fibrosis (CF) in patients aged six years and older who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene to include other gating (class III) mutation in the CFTR gene.

### 2 Requested listing

- 2.1 The submission proposed listing for the treatment of patients with non-G551D mutations under whichever scheme (PBS or Life Saving Drugs Programme) considered appropriate by the PBAC. As no restriction was presented in the minor submission, the restriction proposed for the March 2014 PBAC meeting is presented below:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
IVACAFTOR Tablet 150 mg	56	2	Kalydeco Vertex

Section 100 (Highly Specialised Drugs Program)

Authority required

OR

Life Saving Drugs Program

Treatment of cystic fibrosis in patients age six years or older who have a confirmed class III (gating) mutation in the CFTR gene.

### 3 Background

- 3.1 Ivacaftor was listed on the Australian Register of Therapeutic Goods (ARTG) on 14 August 2014 "...for the treatment of cystic fibrosis (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 TGA registered for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene.
- 3.2 The PBAC considered a major submission for ivacaftor in July 2013. The PBAC noted that it may be possible to reduce the dose of ivacaftor in clinical practice by co-administering ivacaftor with a strong CYP3A inhibitor, but that even with a dose reduction, the cost per QALY would remain too high. The PBAC decided to defer

making a recommendation to allow the sponsor the opportunity to consider the Committee's views and to submit a new price proposal for PBS listing.

- 3.3 In November 2013 the PBAC considered a minor submission in which the sponsor indicated it was not supportive of a regimen of co-administering ivacaftor with a strong CYP3A inhibitor. The PBAC noted however that CYP3A4 inhibitors such as macrolide antibiotics are an appropriate option as boosting agents where a patient already requires these inhibitors as part of their standard CF management. The PBAC considered that patients requiring prophylactic antibiotics could plausibly comprise a substantial proportion of CF patients.
- 3.4 In November 2013 the PBAC recommended ivacaftor for listing. 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) would be around \$60,000-80,000 per quality-adjusted life-years gained, and if certain risk-sharing arrangements were implemented.
- 3.5 The PBAC also considered that it would be necessary to put in place with the sponsor arrangements for data collection, and ensure the implementation of assumptions regarding reduction in the price of ivacaftor that was included in the sponsor's model.
- 3.6 The PBAC considered a major submission for ivacaftor in March 2014, requesting listing for patients with any Class III gating mutation of the CFTR gene. The PBAC recalled that the previous submission had requested listing only for patients with a G551D mutation of the CFTR gene. The PBAC reiterated its previous recommendation for the PBS listing of ivacaftor as a Section 100 (Highly Specialised Drugs Program) benefit for treatment of CF in patients aged six years and older who have a G551D mutation in the CFTR gene.
- 3.7 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 noted 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 it would consider amending the restriction to include those patients at that time.

#### **4 Clinical place for the proposed therapy**

- 4.1 Ivacaftor is intended to be used as add on to current best supportive therapy, and has a different mechanism of action to the antibiotics and mucolytics currently available through the PBS. Under the proposed listing, CF patients aged 6 and over with a G551D or other gating (class III) mutation in the CFTR gene will be eligible for ongoing ivacaftor therapy.

## 5 Comparator

5.1 As a minor submission, there was no economic comparison.

## 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 minor submission presented the following clinical trial:

#### Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
KONNECTION	Clinical Study Report: A Phase 3, Two-part, Randomized, Double-blind, Placebo-controlled, Crossover Study With an Open-label Period to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have a Non-G551D-CFTR Gating Mutation (Version 2)	14 May 2014

6.4 KONNECTION was a Phase 3, two-part, randomized, double-blind, placebo-controlled, 8-week crossover study (Part 1) with a 16-week open-label period (Part 2) of orally administered ivacaftor in subjects with CF. This study enrolled subjects who were age 6 years and older and who have a non-G551D-CFTR gating mutation (n = 39). The patients included in KONNECTION had one of 9 non-G551D-CFTR gating mutations i.e. G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P or G1349D.

6.5 In the March 2014 submission, details of the KONNECTION trial were provided as a poster presentation (Appendix 4 of the resubmission) and the full Clinical Study Report (Version 1, 11 September 2013).

6.6 The minor submission compared the outcomes of the KONNECTION trial with the STRIVE and ENVISION trials. The July 2013 submission presented two randomised trials comparing ivacaftor with Best Supportive Care in patients with CF involving a G551D mutation in the CFTR gene. These are the STRIVE trial (n=161, patients aged 12 years and over) and the ENVISION trial (n=52, patients aged 6-11), both of which ran for 48 weeks.

### Comparative effectiveness and harms

6.7 The primary efficacy endpoint of the KONNECTION trial was the absolute change from baseline in percent predicted forced expiratory volume in 1 second (FEV1)

through Week 8 in each period of Part 1. The submission states the results show clinically meaningful and statistically significant improvements in the primary and secondary endpoints.

- 6.8 The submission stated in KONNECTION, the proportion of subjects with adverse events was lower during ivacaftor treatment (73.7%) than during placebo treatment (83.8%). The safety data were consistent with the other phase III trials of ivacaftor and no new safety signals were observed.
- 6.9 The submission presented a comparison of the KONNECTION trial (at week 8) with the STRIVE and ENVISION trials (in CF patients with G551D mutations, week 24 and 48) to support the proposed change to the restriction.

Efficacy results for G551D patients (STRIVE and ENVISION) and non-G551D patients (KONNECTION)

		Absolute change from baseline in %predicted FEV1	Absolute change from baseline in sweat chloride	Time to first pulmonary exacerbation	Absolute change from baseline in weight	Absolute change from baseline in CFQ-R
Trial	% predicted FEV1 at screening	Treatment effect difference: % (95%CI)	Treatment effect difference: mmol/L (95% CI):	Hazard ratio	Treatment effect difference: kg (95%CI)	Treatment effect difference: units (95%CI)
STRIVE <u>To Week 24:</u>	40% to 70%	10.58 (8.57, 12.59) P < 0.0001	-47.93 (-51.34, -44.52) P < 0.0001	0.399 (0.225, 0.706) P = 0.0016	2.75 (1.76, 3.74) P < 0.0001	8.08 (4.73, 11.42) P < 0.0001
<u>To Week 48:</u>		10.50 (8.50, 12.50) P < 0.0001	-48.07 (-51.47, -44.68) P < 0.0001	0.455 (0.282, 0.733) P = 0.0012	2.71 (1.33, 4.09) P = 0.0001	8.60 (5.32, 11.87) P < 0.0001
ENVISION <u>To Week 24:</u>	40% to 105%	12.45 (6.56, 18.34) P < 0.0001	-54.32 (-61.83, -46.82) P < 0.0001	N/A	1.90 (0.86, 2.94) P = 0.0004	5.93 (0.50, 11.36) P = 0.0330
<u>To Week 48:</u>		9.99 (4.52, 15.47) P = 0.0006	-53.47 (-60.92, -46.02) P < 0.0001		2.77 (1.31, 4.23) P = 0.0002	4.88 (-0.44, 10.20) P = 0.0713
KONNECTION <u>To Week 8:</u>	>40%	10.678 (7.256, 14.100) P<0.0001	-49.167 (-56.953, -41.380) P<0.0001	N/A	1.667 (0.710, 2.626) P=0.0007	9.611 (4.487, 14.734) P=0.0004

Source: Table 7 of the minor submission

CI = confidence interval

CFQ-R = the respiratory domain of the Cystic Fibrosis Questionnaire-Revised

## Clinical claim

- 6.10 The submission claimed that in the KONNECTION trial, ivacaftor has superior comparative effectiveness compared with placebo.
- 6.11 The submission claimed that the efficacy and safety of ivacaftor in non-G551D patients is equivalent to that in G551D patients.
- 6.12 The submission claimed that ‘overall, a range of clinical trials including a range of gating mutations, demonstrates the effectiveness of ivacaftor across an array of clinically relevant pulmonary and non-pulmonary endpoints. The results of all phase III trials (STRIVE, ENVISION and KONNECTION) were consistent with regard to improvements in percent predicted FEV1 and weight gain.’

### **Economic analysis**

- 6.13 As a minor submission, there is no economic comparison presented.

### **Estimated PBS usage & financial implications**

- 6.14 The minor submission stated that ‘The Australian Cystic Fibrosis Data Registry Annual Report 2012 identifies 5 patients with non-G551D mutations. (Correspondence with the ACFDR suggested that number is expected to slightly increase; hence in the November 2013 Major Resubmission Vertex included the estimate of approximately 10 patients.)’
- 6.15 The Commentary [7.6 COM.48] of the March 2014 major submission stated that the estimates reported in the resubmission do not include the non-G551D class III (gating) mutation category. This is explained in Table E.1.1 of the submission, which states that these [REDACTED] in Section F.
- 6.16 The pre-PBAC response of the March 2014 submission proposed [REDACTED] as per the original submission for G551D alone and reiterated that [REDACTED].
- 6.17 The sponsor noted ‘Since the minor submission for the November 2014 PBAC meeting several additional patients with a gating (class III) mutation in the CFTR gene other than G551D have been identified as a consequence of a CFTR mutation testing program’. [REDACTED].
- 6.18 Estimated financial implications were not presented in the Minor Submission.

## **7 PBAC Outcome**

- 7.1 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 cystic fibrosis (CF) in patients aged six years and older who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene to include other gating (class III) mutation in the CFTR gene.



**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.