

# **Ivacaftor for cystic fibrosis: Predicted versus actual analysis**

## **Drug utilisation sub-committee (DUSC)**

*February 2018*

### **Abstract**

#### ***Purpose***

To compare the predicted and actual utilisation of ivacaftor for cystic fibrosis (CF) since Pharmaceutical Benefits Scheme (PBS) listing on 1 December 2014.

#### ***Listing on the Pharmaceutical Benefits Scheme (abridged)***

Cystic fibrosis patients with a G551D mutation in the CFTR gene on at least 1 allele, or another gating (class III) mutation in the CFTR gene on at least 1 allele.

To qualify for initial PBS therapy, a patient must have a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis.

For the full restriction, refer to the PBS schedule.

#### ***Data Source***

Department of Human Services (DHS) PBS prescription data for dates of supply from 1 December 2014 to 30 September 2017, inclusive.

#### ***Key Findings***

- Since its listing in December 2014, a total of 268 patients have been supplied ivacaftor for CF.
- The number of patients treated with ivacaftor in each of the first two years of listing was less than predicted. This may be due to an overestimation of the proportion of the CF population having a G551D mutation.
- The number of prescriptions per patient was higher than predicted. This may be due to higher adherence and/or less dose reduction for patients with hepatic impairment or concomitant CYP3A4 inhibitor use than anticipated.
- Overall expenditure was close to that predicted in the submission (notwithstanding performance rebates).

## Purpose of analysis

To compare the predicted and actual utilisation of ivacaftor for cystic fibrosis since it was PBS listed for this indication on 1 December 2014.

## Background

### Clinical situation

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane regulator (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 (lungs, pancreas, intestinal tract, biliary tract, sweat glands, and reproductive tract).<sup>1</sup>

CF in Australia is predominantly diagnosed by the Newborn Screening Program, a heel-prick blood sample taken on day three or four of life. The majority of patients with CF are diagnosed before 12 months of age.<sup>2</sup> Infants with two CF mutations are referred directly to a specialist CF centre.<sup>3</sup>

Many patients with CF are now surviving into adulthood, with improvements in respiratory and nutritional management increasing median survival to over 35 years of age.<sup>3</sup> In 2014, the estimated number of patients in Australia with CF was over 3,000.<sup>2</sup>

There are a range of identified CFTR mutations, with around 50% of patients identified as having a F508 deletion. G551D mutation is the second most common identified, with a prevalence of 231 patients (7.6%) in 2014.<sup>2</sup>

Conventional treatment options for CF include antibiotics, osmotic agents, bronchodilation, mucolytics, pancreatic enzymes, diet therapy and chest physiotherapy. Ivacaftor is used as an add-on to conventional therapy for CF patients with a G551D mutation.

### Pharmacology

Ivacaftor is a selective potentiator of the CFTR protein that improves the function of the CFTR protein in patients with CF expressing the G551D mutation and acts by enhancing chloride transport.<sup>4</sup>

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<sup>1</sup> Ivacaftor, Public Summary Document, July 2013, Available from

<<http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-07/ivacaftor>>

<sup>2</sup> Cystic Fibrosis Australia 2014. 17<sup>th</sup> Annual Report Australian Cystic Fibrosis Data Registry. Available from <[www.cysticfibrosis.org.au/data-registry](http://www.cysticfibrosis.org.au/data-registry)>

<sup>3</sup> Cystic Fibrosis [revised 2015 Mar]. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2017 Nov.

<sup>4</sup> Kalydeco® (ivacaftor). Australian Approved Product Information. St Leonards: Vertex Pharmaceuticals (Australia) Pty Ltd. Approved 9 July 2013, updated 16 September 2016. Available from <https://www.tga.gov.au/product-information-pi>

## Therapeutic Goods Administration (TGA) approved indications

Ivacaftor is indicated for the treatment of patients with cystic fibrosis:

- Aged 2 years and older who have a G551D or other gating (class III) mutation in the CFTR gene; or
- Aged 6 years and older who have a R117H mutation in the CFTR gene

## Dosage and administration

The recommended dose for adults, adolescents and children aged 2 years and older is outlined in Table 1.

**Table 1: Dosage of ivacaftor for CF**

| Weight             | Dose              | Total daily dose |
|--------------------|-------------------|------------------|
| < 14 kg            | 50 mg granules bd | 100 mg           |
| ≥ 14 kg to < 25 kg | 75 mg granules bd | 150 mg           |
| ≥ 25 kg            | 150 mg tablet bd  | 300mg            |

bd: Twice daily (every 12 hours)

Source: Table 9, Kalydeco Australian Approved Product Information

When ivacaftor is co-administered with strong inhibitors of CYP3A4,<sup>5</sup> the dose should not exceed one dose twice weekly. When ivacaftor is co-administered with a moderate inhibitor of CYP3A4,<sup>6</sup> the dose should not exceed one dose daily.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

## PBS listing details

Ivacaftor for the treatment of CF was PBS-listed on 1 December 2014. Table 2 provides the PBS listing details as at 1 December 2017.

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<sup>5</sup> Strong inhibitors include boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin and voriconazole

<sup>6</sup> Moderate inhibitors include amprenavir, aprepitant, atazanavir, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib and verapamil.

**Table 2: PBS listing of ivacaftor for CF**

| Item                                    | Name, form & strength, pack size         | Max. quant. | Rpts | DPMQ        | Brand name and manufacturer                             |
|-----------------------------------------|------------------------------------------|-------------|------|-------------|---------------------------------------------------------|
| S100 (Highly Specialised Drugs) Private |                                          |             |      |             |                                                         |
| 10175M                                  | Ivacaftor 150 mg tablet, 56              | 56          | 5    | \$22,547.15 | Kalydeco®<br>Vertex Pharmaceuticals (Australia) Pty Ltd |
| 11109Q                                  | Ivacaftor 75 mg granules, 4 x 14 sachets |             |      |             |                                                         |
| 11097C                                  | Ivacaftor 50 mg granules, 4 x 14 sachets |             |      |             |                                                         |
| S100 (Highly Specialised Drugs) Public  |                                          |             |      |             |                                                         |
| 10170G                                  | Ivacaftor 150 mg tablet, 56              | 56          | 5    | \$22,500    | Kalydeco®<br>Vertex Pharmaceuticals (Australia) Pty Ltd |
| 11098D                                  | Ivacaftor 75 mg granules, 4 x 14 sachets |             |      |             |                                                         |
| 11105L                                  | Ivacaftor 50 mg granules, 4 x 14 sachets |             |      |             |                                                         |

Source: the PBS website. Special Pricing Arrangements apply.

### ***Restriction (abridged)***

Patients must have a G551D mutation in the CFTR gene on at least 1 allele, or another gating (class III) mutation in the CFTR gene on at least 1 allele and be assessed through a cystic fibrosis clinic/centre. To qualify for initial PBS therapy, a patient must have a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis.

Patients must use ivacaftor concomitantly with standard therapy and treatment is not to be given to a patient who has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease in the four weeks prior to commencing therapy.

The PBS restriction specifies that the dose of ivacaftor must not exceed 150 mg twice a week or 150mg once daily if a patient is concomitantly receiving a strong or moderate CYP3A4 inhibitor, respectively. Patients are unable to access PBS-subsidised ivacaftor if concomitantly receiving a CYP3A4 inducer.

For details of the current PBS listing refer to the PBS website.

Written applications for authority to prescribe are submitted to the Department of Human Services (DHS). For the initial application, prescribers are required to confirm that the patient meets all of the PBS criteria and provide a copy of the pathology report demonstrating the G551D mutation in the CFTR gene on at least 1 allele, or another gating (class III) mutation in the CFTR gene on at least 1 allele, and provide the results of the sweat chloride test.

Data collected through the initial and continuing written authority application process includes:

- Weight and height
- Baseline measurement of the number of days of CF-related hospitalisation (including hospital-in-the-home) in the last 12 months (6 months for continuing)
- Forced Expiratory Volume in one second (FEV<sub>1</sub>) for patients aged 6 years or older (measured in an accredited pulmonary function laboratory, with documented no acute infective exacerbation at the time of measurement)
- Concomitant use of CYP3A4 inhibitors and/or inducers

### ***Changes to listing***

A summary of relevant changes to the listing of ivacaftor is shown in Table 3.

**Table 3: Changes to ivacaftor restrictions**

| Date           | Changes to restriction                                                                                                                                                                                                                                                                             |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 June 2015    | Ciprofloxacin was removed from list of moderate CYP3A4 inhibitors that require dose reduction if co-administered with ivacaftor<br><br>Details of requirement to submit to DHS a baseline measurement of number of days of hospitalisation was amended to specify only CF-related hospitalisations |
| 1 October 2015 | Prednisone was removed from the list of weak CYP3A4 inducers that precludes patients from receiving PBS-subsidised ivacaftor.                                                                                                                                                                      |
| 1 May 2017     | Population expanded to include children aged 2-5 years.<br><br>Granule formulation added.                                                                                                                                                                                                          |

Current PBS listing details are available from the PBS website.

### **Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)**

Seven submissions for ivacaftor for the treatment of CF have been considered by the PBAC, with the first positive recommendation for PBS listing made at the November 2013 meeting. At that time, the PBAC considered that the cost-effectiveness of ivacaftor would be acceptable if the incremental cost-effectiveness ratio (ICER) was between \$60,000 and \$80,000 per quality-adjusted life-years gained and if a risk sharing agreement was entered into which included a cap on patient numbers with 100% rebates beyond the agreed patient numbers.

In a subsequent consideration in March 2014, the base case ICER presented in the resubmission was more than \$100,000 per QALY gained. The PBAC remained of the view, previously expressed in November 2013, that the cost-effectiveness of ivacaftor would be acceptable if the ICER was between \$60,000 and \$80,000 per QALY gained. The PBAC considered that, in the absence of a lower price, the cost-effectiveness of ivacaftor could be improved under a “pay for performance” arrangement, added to other risk sharing measures previously recommended. [REDACTED]

[REDACTED]

In November 2014, the PBAC extended the recommendation for PBS listing to include other gating (class III) mutations in the CFTR gene [REDACTED]

Subsequent to the November 2016 PBAC meeting, in January 2017, the PBAC recommended the listing of ivacaftor be extended to include patients aged 2-5 years and recommended the addition of a new granule formulation of ivacaftor. [REDACTED]

For further details, refer to the Public Summary Documents from the July 2013, November 2013, March 2014, November 2014, July 2015, November 2015, and November 2016 meetings.

### **Approach taken to estimate utilisation**

The modelling steps used to derive the utilisation and cost of ivacaftor to the PBS is presented in Appendix 1.

The submission presented an epidemiological approach to estimate utilisation of ivacaftor for CF. The approach to estimate the number of patients treated was based on data from the Australian Cystic Fibrosis Data Registry, with data collected from 22 specialist CF clinics across Australia. The number of patients aged 6 years older with at least one copy of a G551D-CFTR genetic mutation in 2011 was [REDACTED], corresponding to a prevalence rate of [REDACTED]. The submission adjusted this estimate to [REDACTED] to account for people over 30 years of age who may not have undergone genotypic screening.

The PBAC considered that the submission's estimates of the number of patients treated was reasonable, but noted that there was a potential for leakage into other subgroups of CF patients given the biological plausibility that ivacaftor would be effective in some of those subgroups.

The total projected costs were calculated by multiplying the forecasted number of patients by [REDACTED] prescriptions per year to account for an adherence rate of [REDACTED] to account for moderate or severe hepatic impairment or CYP3A4 inhibitor use. The dose adjustment was estimated from a clinician survey. These assumptions were uncertain.

The submission assumed 100% of prevalent and incident patients with a G551D mutation would commence therapy and a discontinuation rate of 0%.

When the PBAC recommended expanding the eligible population to include patients with other gating (class III) mutations, patient numbers for the purpose of the cap were not changed. When the patient population was expanded to include children aged 2-5 years, patient caps were [REDACTED].

## Methods

PBS prescription data for all ivacaftor PBS item codes were extracted from the Department of Human Services (DHS) prescription database for date of supply from December 2014 (the month ivacaftor was listed on the PBS) to the end of September 2017. The data was extracted on 11 December 2017. There are six PBS item code for ivacaftor (10170G, 10175M, 11097C, 11098D, 11105L and 11109Q), all of which are indicated for the treatment of cystic fibrosis with G551D mutation.

PBS prescription data were used to determine the number of prescriptions supplied and the PBS expenditure. These data were also used to count the number of patients, both incident (new to treatment) and prevalent (number treated in each time period, i.e. year or quarter). Patients were considered incident to PBS treatment at their first prescription in the data, which starts at the date of PBS listing 1 December 2014.

When ivacaftor was first listed on the PBS there was a separate restriction for grandfathered patients. Grandfathered patients (i.e. received non-PBS ivacaftor prior to PBS ivacaftor) are not distinguished in this analysis.

An analysis of scripts per patient in the 12 months after initiation to PBS ivacaftor was also performed. This analysis was limited to the cohort of patients that had at least 12 months of follow-up data after initiation. That is, patients that initiated from December 2014 to the end of September 2016.

## Results

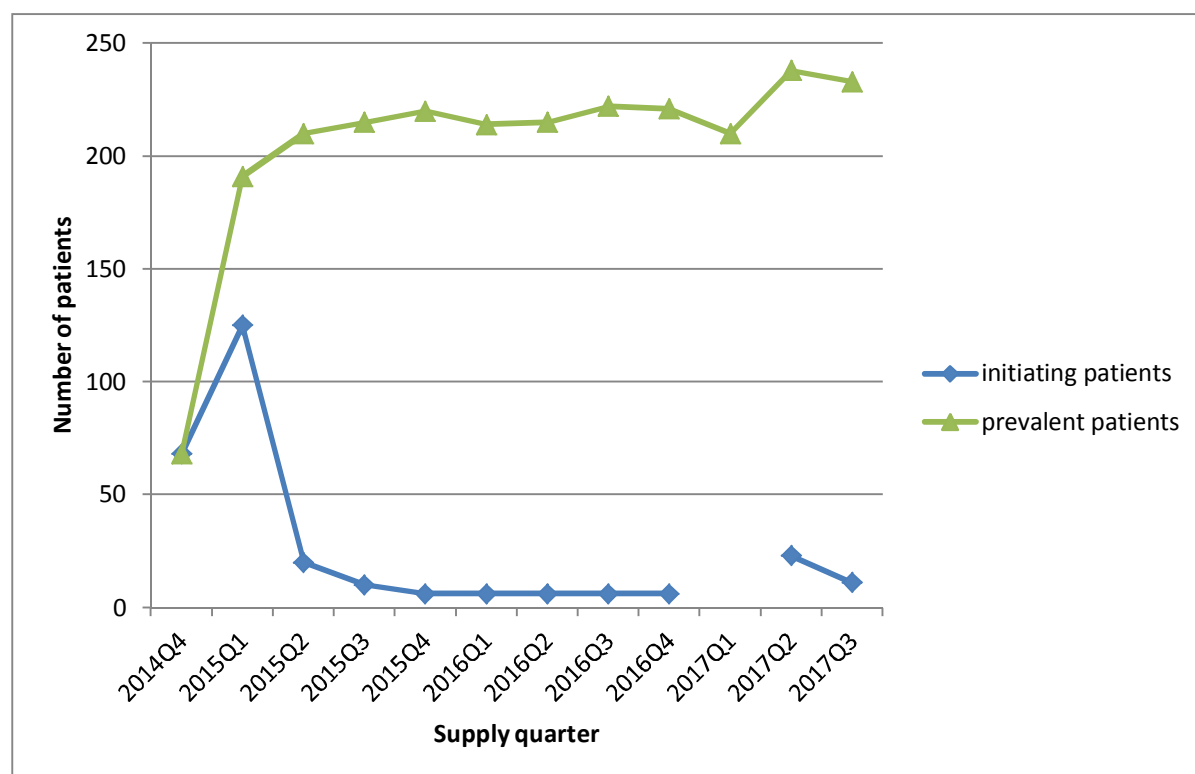
### Analysis of drug utilisation

#### *Overall utilisation*

Figure 1 shows the total number of patients who were supplied ivacaftor in each quarter and of those patients, those that received their first ever PBS supply of ivacaftor in that quarter. Initiating patients include people receiving supply under the initial treatment restriction and the grandfather restriction. While grandfathered patients are continuing ivacaftor treatment, they are new to PBS supply.

Following PBS listing, a large proportion of the total number of patients received their first PBS supplied prescription of ivacaftor. The number of new patients being treated with ivacaftor since this time has remained low. There was a slight increase in initiating patients in the second quarter of 2017 as a result of the population expanding to children aged

2-5 years. A total of 268 unique patients have been supplied ivacaftor from the time of PBS listing (1 December 2014) to the most recent data (30 September 2017).



**Figure 1: Initiating patients and total number of patients supplied ivacaftor**

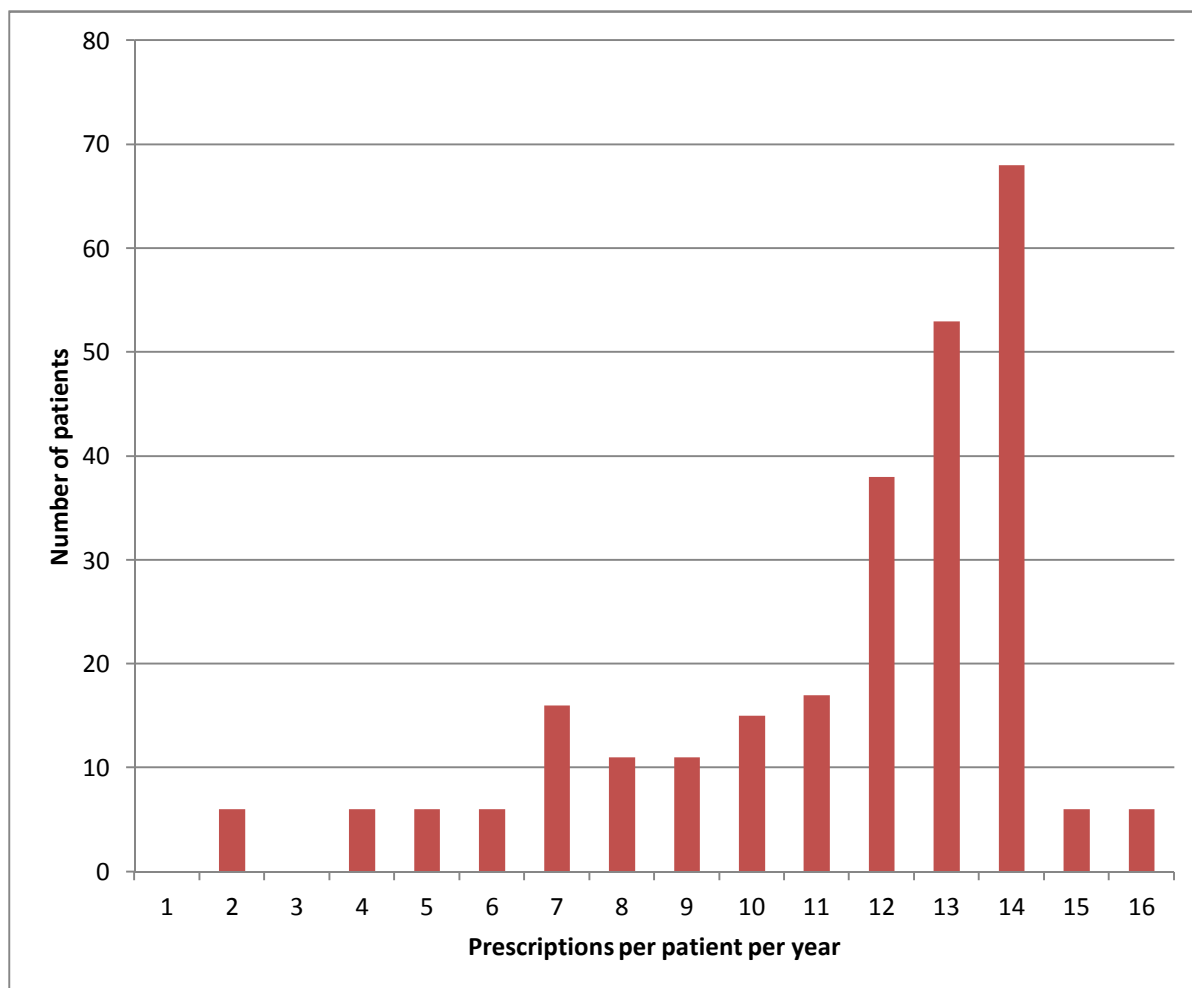
Data are presented by quarter of supply. Initiators are total number of people supplied their first PBS-subsidised prescription; this is a subset of PBS patients. There were no new patients in the first quarter of 2017. Data points that equal 6 may represent 6 or fewer patients.

The average number of prescriptions per patient per year at an aggregate level is shown in Table 4.

**Table 4: Aggregate prescriptions per patient per year**

|                           | Year 1 | Year 2 |
|---------------------------|--------|--------|
| Prescriptions             | 2,211  | 2,384  |
| Patients                  | 225    | 230    |
| Prescriptions per patient | 9.83   | 10.37  |

The distribution of the number of prescriptions per patient per year, based on individual patient data for the first 12 months post-initiation, is shown in Figure 2 and indicates that the majority of patients received between 12 and 14 prescriptions per year.



**Figure 2: Distribution of the number of packs per individual patient in their first year of PBS treatment.**

Data points that equal 6 may represent 6 or fewer patients.

An analysis of patients who have at least two years of data available from their first PBS supply shows that the majority of patients received 12-13 prescriptions in the second year (data not shown).

### Analysis of expenditure

\$149.7 million in PBS benefits have been paid for ivacaftor since its listing on 1 December 2014 (Table 5).

**Table 5: Government cost (Benefits paid) for ivacaftor for the treatment of CF**

| Year                                    | PBS benefits         |
|-----------------------------------------|----------------------|
| Year 1 (December 2014 – November 2015)  | \$49,695,770         |
| Year 2 (December 2015 – November 2016)  | \$53,607,327         |
| Year 3 (December 2016 – September 2017) | \$46,430,155         |
| <b>Total</b>                            | <b>\$149,773,252</b> |

## Analysis of actual versus predicted utilisation

A comparison of the predicted utilisation of ivacaftor versus actual use is shown in Table 6.

**Table 6: Comparison of the predicted versus actual utilisation of ivacaftor for the treatment of cystic fibrosis**

| Parameter                                            | Comparison     | Year 1 (December 2014 – November 2015) | Year 2 (December 2015 – November 2016) |
|------------------------------------------------------|----------------|----------------------------------------|----------------------------------------|
| Treated patients                                     | Predicted      |                                        |                                        |
|                                                      | Actual         | 225                                    | 230                                    |
|                                                      | % of predicted |                                        |                                        |
| Number of prescriptions                              | Predicted      |                                        |                                        |
|                                                      | Actual         | 2,211                                  | 2,384                                  |
|                                                      | % of predicted |                                        |                                        |
| Average number of prescriptions per patient per year | Predicted      |                                        |                                        |
|                                                      | Actual         | 9.83                                   | 10.37                                  |
|                                                      | % of predicted |                                        |                                        |
| Overall expenditure                                  | Predicted      |                                        |                                        |
|                                                      | Actual         | \$49,695,770                           | \$53,607,327                           |
|                                                      | % of predicted |                                        |                                        |

Source: The predicted figures were sourced from the financial estimates model agreed with the sponsor

## Pay for performance arrangement

The PBAC recommended pay-for-performance arrangements whereby the sponsor would rebate the Commonwealth [REDACTED] of the cost of treatment with ivacaftor received by patients who were subsequently assessed as not responding to treatment. Analysis of these arrangements is ongoing. The overall expenditure reported in Table 6 is expenditure prior to rebates.

## Discussion and DUSC consideration

The number of patients treated with ivacaftor in the first two years of listing was lower than predicted. This may be due to an overestimated proportion of the CF population having a G551D mutation. The Cystic Fibrosis Data Registry Report (2014) noted that 7.6 per cent of the CF population have a G551D mutation, compared to the submission's estimate of [REDACTED]. The original submission justified this difference on the assumption that patients over 30 years of age may not have undergone genotypic screening and therefore adjusted the prevalence of G551D mutation in this population upwards to match younger patients. DUSC noted the Australian cystic fibrosis data registry (ACFDR) 2015 report was released in October 2017. The findings were similar to the 2014 report.

The submission anticipated that patients would use an average of [REDACTED]. Actual use was higher than predicted with an average of [REDACTED]. DUSC considered the assumption of [REDACTED] adherence was underestimated. The distribution of the actual number of dispensed packs per patient demonstrates that the majority of patients receive between 12 and 14 prescriptions per

year. The assumption that there would be a net dose reduction of [REDACTED] due to less frequent dosing of ivacaftor in patients with hepatic impairment or concomitant CYP3A4 inhibitor use, was derived from a clinical survey, and was uncertain. Data from the DHS authorities database for the first twelve months of listing of ivacaftor (1 December 2014 – 30 November 2015) indicates that of the 625 authority approvals processed, five of these recorded concomitant use of a strong CYP3A4 inhibitor and one recorded concomitant use of a moderate CYP3A4 inhibitor. DUSC considered the registry data regarding CYP inhibitors may be incomplete, as the proportion of people using concomitant CYP inhibitors in this patient group is expected to be higher; e.g. antifungal use. The proportion of patients with hepatic impairment was not differentiated in the clinician survey and is not recorded in the DHS Authorities database.

The sponsor noted that, in aggregate, the PBS expenditure is extremely consistent with what was predicted in the submissions [REDACTED].

## **DUSC Actions**

- DUSC requested that the report be provided to the PBAC

## **Context for analysis**

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

## **Sponsors' comments**

Vertex Pharmaceuticals (Australia) Pty Ltd: The sponsor has no comment

## **Disclaimer**

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any

given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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## Appendix 1: Derivation of the forecasted utilisation of ivacaftor

| Model step                                      | Parameter                                                                                    | Baseline | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|-------------------------------------------------|----------------------------------------------------------------------------------------------|----------|--------|--------|--------|--------|--------|
| <b>A. Derivation of the eligible population</b> |                                                                                              |          |        |        |        |        |        |
| [A.1]                                           | Number of CF patients in Australia <sup>1</sup>                                              |          | ■      | ■      | ■      | ■      | ■      |
| [A.2]                                           | New cases of CF in population ≥ 6 years <sup>1</sup>                                         |          | ■      | ■      | ■      | ■      | ■      |
| [A.3]                                           | Prevalence of G551D mutation <sup>1</sup>                                                    | 8.6%     |        |        |        |        |        |
| [A.4] = [A.2] x [A.3]                           | <b>Eligible population<sup>2</sup></b>                                                       |          | ■      | ■      | ■      | ■      | ■      |
| <b>B. Number of R/PBS prescriptions</b>         |                                                                                              |          |        |        |        |        |        |
| [B.1]                                           | Packs dispensed per patient per year <sup>3</sup>                                            | 11.8     |        |        |        |        |        |
| [B.2] = [B.1] x [A.4]                           | Total number of packs                                                                        |          | ■      | ■      | ■      | ■      | ■      |
| [B.3]                                           | Percentage reduction in dose to reflect hepatic impairment and CYP3A inhibitors <sup>4</sup> | ■        |        |        |        |        |        |
| [B.4] = [B.2] x (1-[B.3])                       | Total dispensed packs reduced to reflect dose adjustments                                    |          | ■      | ■      | ■      | ■      | ■      |
| <b>C. R/PBS expenditure</b>                     |                                                                                              |          |        |        |        |        |        |
| [C.1]                                           | Dispensed price maximum quantity <sup>5</sup>                                                | \$22,500 |        |        |        |        |        |
| [C.2] = [C.1] x [B.4]                           | Total cost for ivacaftor                                                                     |          | ■      | ■      | ■      | ■      | ■      |
| [C.3] = [B.4] x \$11.72                         | Patient contributions                                                                        |          | ■      | ■      | ■      | ■      | ■      |
| [C.4] = [C.2] - [C.3]                           | <b>Cost of drug to the R/PBS</b>                                                             |          | ■      | ■      | ■      | ■      | ■      |

<sup>1</sup> Australian Cystic Fibrosis Data Registry 2011

<sup>2</sup> Assumption that 100% of eligible population would be treated and 0% discontinuation

<sup>3</sup> Based on 90.6% adherence rate

<sup>4</sup> Based on a clinician survey

<sup>5</sup> Published price. Special pricing arrangements apply.