TAR 400 – Ivacaftor for cystic fibrosis with the G551D mutation (February 2020 update)

This assessment provides an update to earlier economic analyses undertaken by PHARMAC staff, as documented in TAR 236 (June 2014; A700506) and TAR 318 (May 2018; A1138483). Both earlier TARs document the steps undertaken by PHARMAC staff in evaluating a supplier provided cost-effectiveness model for ivacaftor in cystic fibrosis patients with the G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This TAR provides an update to this earlier work, primarily incorporating the outcomes of recent negotiations with the supplier (Vertex Pharmaceuticals). This TAR does not re-evaluate the evidence base underpinning the earlier economic assessment.

A mutation in the CFTR gene is disease defining for cystic fibrosis, an autosomal recessive disorder characterised by the expression of a dysfunctional chloride channel involved in the normal production of mucus across epithelial membranes. Patients with cystic fibrosis produce only highly viscous mucus, resulting in severe damage to organ systems where homeostatic function is dependent on normal 'watery' mucus being available. These organ systems include the respiratory tract, as well as the digestive and reproductive systems.

Affected individuals are subject to considerable morbidity throughout their lifetime, experiencing a range of health problems including recurrent respiratory infections, pancreatic insufficiency, malnutrition, and infertility. Patients are also subject to a high rate of diabetes during their lifetime.

Greater understanding of cystic fibrosis has enabled improvements of quality of care and survival over recent decades, with a greater proportion of affected patients surviving into adolescence and adulthood. However, affected individuals still experience a high rate of premature mortality. The average life-expectancy of cystic fibrosis patients in New Zealand is currently unknown with certainty, though has been suggested by Cystic Fibrosis New Zealand (a patient advocacy society) to be as low as 37 years of age.

Ivacaftor is an oral therapy licenced for use with patients with a specific ATP-gating defect in the CFTR protein, known as the G551D mutation. Patients with the G551D mutation still produce CFTR chloride channels that reach the apical cell surface, albeit with a lower probability of opening compared to normal. The ability to transport chloride across the membrane is considerably reduced, resulting in less water crossing the epithelial membrane surface, and increased mucus viscosity. Ivacaftor is suggested to help restore the normal function of G155D mutated CFTR chloride channels, by binding directly to the channel to increase the probability of opening.

PHARMAC staff estimate that the current cost effectiveness is likely to be within the range of Wit QALYs per $1 million spent, with anticipated budgetary impact of Withhel million over five years (net present value). A summary of the proposal is provided in the table below.

PROPOSAL OVERVIEW
Pharmaceutical Ivacaftor (Kalydeco™) Film coated tablets, each containing 150mg of ivacaftor. Each pack contains 56 tablets, in either blister pack or child-resistant bottle with desiccant.
Supplier Vertex Pharmaceuticals (Australia)
Proposed Indication Treatment of cystic fibrosis in patients aged 6 years and older who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.
Dosing Recommended regimen is 150mg taken orally every 12 hours with a fat-containing meal or snack (300mg per day). Treatment is lifelong.
Pharmaceutical Price Gross pricing of Withheld per pack of 56 tablets (150mg per tablet) Net pricing of Withheld per pack of 56 tablets (150mg per tablet) Net pricing of Withh per patient per day (Withheld per year) Source of pricing: A1352614 (January 2020)
PTAC PRIORITY PTAC reviewed this proposal at the February 2018 meeting where a low recommendation was provided.
PHARMConnect Reference Ivacaftor (Kalydeco) for cystic fibrosis, G551D mutation.

1. Proposal Overview

1.1 Summary

An application for the funding of ivacaftor for the treatment of cystic fibrosis with G551D mutation was received from Vertex Pharmaceuticals (Australia) Pty Ltd in February 2014.

Clinical advice was sought from the Respiratory Subcommittee at the April 2014 meeting where it was recommended this proposal be deferred until longer term evidence was presented that enabled determination of survival benefit.

A call for applications for rare disorders by PHARMAC in September 2018 resulted in an updated submission from Vertex Pharmaceuticals. Clinical advice was received from the Rare Disorders Subcommittee at the November 2018 meeting, whereby this proposal was recommended for funding with a medium priority based on high health need, lack of disease modifying treatment options and moderate quality of evidence. PTAC further reviewed this proposal at the February 2019 meeting, recommending a low priority, noting the limited availability of long-term data, markers of surrogacy and high cost.

The table below provides a summary of the patient population; intervention; comparator treatment; and main outcomes of treatment.

Table 1. PICO as used in this economic analysis.

PICO	
POPULATION	Cystic fibrosis patients with G551D gating mutation
INTERVENTION	Ivacaftor 150mg orally twice daily (300mg per day)
COMPARISON	Best supportive care
OUTCOME	Maintenance of force expiratory volume in 1 second (FEV1), reduction of health care utilisation

1.2 Patient Population

Disease description

Cystic fibrosis (CF) is an autosomal recessive disease characterised by abnormal airway secretions, chronic endobronchial infection, and progressive airway obstruction. It is characterised by abnormal transport of sodium and chloride across an epithelium leading to the formation of thick, viscous secretions.

Cystic fibrosis is caused by a mutation in a gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR regulates the movement of chloride and sodium ions across epithelial membranes, such as the alveolar epithelia located in the lungs. CF is caused by mutations in CFTR that affect the quantity of protein that reaches the cell surface or that affect the function of the CFTR channels at the cell surface. More than 1900 CTFR gene mutations have been identified which are assigned to one of five classes depending on their functional outcomes.

Class III gating mutations

About 4% of patients with cystic fibrosis worldwide have the Class III (gating) mutation, G551D on at least one allele. This type of mutation results in a CFTR protein that is present in the apical cell membrane but displays greatly reduced chloride transport (Bompadre et al. J Gen Physiol. 2017; 129(4):285-298).

From birth patients experience organ damage, including pancreatic insufficiency and progressive loss of lung function, ultimately resulting in respiratory failure and premature death. Extra-pulmonary manifestations also include bone disease, cystic fibrosis related liver disease, reproductive tract problems and diabetes.

Signs and symptoms of cystic fibrosis include poor growth and poor weight gain despite normal food intake, accumulation of thick, sticky mucous resulting in frequent chest infections and coughing and shortness of breath.

Additional gating (class III) mutations in the CFTR gene include: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R. There are few published reports on the clinical features of patients with other non-G551D gating mutations; however, an analysis of the US CF Foundation Patient Registry data revealed that the rates of lung disease progression in patients with these mutations are similar to that of patients with the G551D mutation.

Epidemiology

According to the Port CFNZ National data registry 2014, there are 443 patients in New Zealand diagnosed as having cystic fibrosis. Of these, 30 (6.8% of the population with CF) have the G551D gene mutation. It is estimated that there would be 23 patients with the G551D gene mutation that would be aged 6 years or greater. Of these patients, it is estimated that 2 patients would be of Māori or Pacific Island descent.

1.3 Current Treatment in New Zealand

Best supportive care (BSC) for New Zealand patients with CF is limited to symptomatic treatments that address disease manifestations but may no longer offer incremental survival benefits independent of natural background medical understanding and advancement. As the disease progresses, patients require more intensive healthcare that includes home-based care, medications, and more frequent and prolonged hospital admissions (van Gool K. et al. Value Health. 2013;16(2):345-55).

The aim of treatment is to maintain lung function at a rate as near to normal as possible. This is usually managed by controlling respiratory infections, clearing airways of mucus, and nutritional therapy. Patients who have mild acute pulmonary exacerbations can be treated at home with inhaled bronchodilator treatment, chest physiotherapy, postural drainage and the use of oral antibiotics.

Cystic fibrosis is characterised by chronic infections with multiple organisms (Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa etc.) requiring the use of antibiotics both orally or nebulised. Azithromycin is commonly prescribed for CF patients and tobramycin is frequently prescribed as nebulised treatment.

Oral pancreatic enzyme therapy is used in patients when the pancreas is not working correctly and aids digestion, mitigating the malnutrition and gastrointestinal symptoms characteristic of pancreatic malfunction.

Patients have individualised treatments to suit their needs; some patients would receive all the following treatments; whereas, others might only receive two or three. Current treatments include:

- inhaled hypertonic saline;
- dornase alfa[1]
- inhaled bronchodilators;
- oral and inhaled steroids;
- regular antibiotics (oral, intravenous or nebulised);
- digestive enzymes;
- vitamin supplements; and
- regular physiotherapy.

1.4 Intervention

Ivacaftor is classified as a CFTR potentiator. The CFTR protein is a chloride channel found in the surface of epithelial cells throughout the body. Mutation of the CFTR gene may result in a reduced number of CTFR channels at the apical surface, impaired channel function or both.

The G551D-CTFR mutation results in defective channel opening or gating, in response to cellular signals. Ivacaftor facilitates increased chloride transport by increasing the

[1] Dornase alfa is available under Special Authority following approval by the Cystic Fibrosis Advisory Panel.

probability of the CFTR channels opening. In vitro studies utilising CF human bronchial epithelial cells positive for the G551D mutation have shown that ivacaftor increases stimulated chloride secretion and also reduces excessive sodium and fluid absorption, preventing dehydration of the airway surface liquid and improving cell motility (Condren et al, J Pediatr Pharmacol Ther. 2013;18(1):8-13)

2. Health Benefits

2.1 Clinical Evidence

A summary of evidence provided in support of this proposal is outlined both in table 2 of the Health Benefit section of the February 2019 PTAC discussion paper. This evidence includes the phase III randomised control trials, STRIVE (Ramsey et al NEJM 2011;365:1663-72) and ENVISION (Davies et al. Am J Respir Crit Care Med 2013;187,11:1219-1225).

2.2 Review of Clinical Evidence

This TAR does not review the clinical evidence used to inform the price update to the results from the economic analysis as reported here. For a review of PHARMAC's consideration of the clinical evidence, please refer to earlier documentation relating to this proposal, including the aforementioned TAR documents, as well as the relevant PTAC and Subcommittee minutes.

3. PHARMAC Cost-Utility Analysis

A cost-utility analysis (CUA) was received from Vertex Pharmaceuticals in Feb 2014 and was evaluated by PHARMAC Staff. This section is an updated analysis of the supplier provided CUA which was provided to PTAC. The only updates to this model undertaken since the publication of the previous TAR 318 have been to account for the earlier entry in the model of generic ivacaftor (anticipated Withheld under) and the significant price reductions negotiated by PHARMAC over the latter half of 2019. All other considerations as outlined in TAR 318 have been retained in this update.

Model Input / Assumption	Details	PHARMAC Comment
Type of analysis	Cost Utility Analysis	Appropriate
Target population	30 New Zealand patients with Cystic fibrosis and the G551D mutation.	Since the previous analysis, there is likely to now be a range of other targeted mutations. This analysis is restricted to G551D as no application has been received for other mutations.
Time horizon	Lifetime.	Appropriate.
Comparator	Standard care	Appropriate. Standard care is a complex bundle of pharmaceuticals and activities. Cystic Fibrosis patients have a high treatment burden. Treatment options for Cystic fibrosis include: antibiotics, inhaled enzymes (Pulmozyme), insulin to manage diabetes, inhalers and mucolytics to open up the airways, steroids to help reduce swelling within the airways, physiotherapy and postural drainage of the chest. A tailored diet (high protein and calories), pancreatic enzymes to help absorb fats and protein vitamin supplements, especially vitamins A, D, E and K. Nasal steroids for, or surgical removal of, nasal polyps. At later stages of disease lung transplants become an option. Lung transplants avoided and the associated benefits to another recipient are excluded from the analysis. It may be reasonable to include these. However, the addition is modest as only 1 transplant is avoided over 4 years in the entire population (0.05 QALYs per patient per year on average).

Model Input / Assumption	Details	PHARMAC Comment
Key Assumptions and inputs	The pivotal assumption is that health using ivacaftor is restored and maintained for the duration of the model.	Not agreed. Our clinical advice from the respiratory subcommittee is that lung function decline would be reduced but not arrested. They state lung function decline *"may be similar to non-CF bronchiectasis, which is approximately half the rate of CF patients".*
Pharmaceutical cost	Gross Pharmaceutical costs (Withhel per patient per year) have been adjusted for both dose adjustments, and adherence. A Wi% price reduction is included in the analysis at patent expiry.	PHARMAC's analysis accepts these estimates.
Non-pharmaceutical cost	A number of medical management costs are included in the model. These include ongoing medical management costs and transplantation. These costs are adjusted based on severity (lung function) and age.	PHARMAC's analysis accepts these estimates.
Health Benefits	The pivotal assumption is that health using ivacaftor is restored and maintained for the duration of the model.	Disagree. Our clinical advice from the respiratory subcommittee is that lung function decline would be reduced but not arrested. They state lung function decline *"may be similar to non-CF bronchiectasis, which is approximately half the rate of CF patients".* Changing this assumption has the effect of halving the benefit in the supplier's model.
Results	The supplier estimates the cost effectiveness as W QALYs per million. Updated for patent expiry, the result is W QALYs per million.	This updated analysis has less time to patent expiry, although halves the benefit as per advice of the Respiratory Subcommittee. The practical impact is to have a lower band of W QALYs per million and an upper band of W QALYs per million. The new upper band is the suppliers model adjusted for a closer time to patent expiry.
Sensitivity analysis	The model's results do not adjust when new assumptions are incorporated.	The provided write up does highlight that the model is sensitive to discounting.

2.3 Summary of Overall Cost-Effectiveness

As outlined above, the base-case QALY per $1m estimate is [redacted]. Taking into account the results of the sensitivity analysis, the highly likely range is estimated to be [redacted]. This range captures the reduction in time to patent expiry since time of last update (May 2018), the potential for full restoration of FEV1 in treated patients (informing the high likely result), and the adjusted rate of FEV1 decline as recommended by clinical advice (informing the low likely result). The possible QALY per $1m range is informed by the **likely range.**

4. Budget Impact Analysis

The 5-year net present value (NPV) to the Combined Pharmaceutical Budget of funding ivacaftor is estimated to be Withheld million, with a cost of the first 12 months of Withheld million. This is outlined in Table 2 below. The 5-year NPV to DHBs is estimated to be Withheld million. All costs are discounted at a rate of 8%.

This BIA assumes a prevalent pool of 30 patients being eligible for ivacaftor in the first year, an incidence of 3% per annum, and uptake of 100% of eligible patients. Patients are assumed to require the full recommended dose (300mg per day). No consideration of net distribution costs informs this BIA as the distribution is expected to occur outside of community pharmacies, incurring no additional cost to the health system. A reduction in health resource utilisation is however anticipated to result in health sector savings for patients treated with ivacaftor, equivalent to $20,000 per patient per year.

Table 2. Net budget impact.

	Year 1	Year 2	Year 3	Year 4	Year 5	5-YR NPV
Patient numbers	30	31	32	33	34	-
Community Pharmaceutical Budget ($mil)	Withheld	Withheld	Withheld	Withheld	Withheld	Withheld
Other DHB Costs ($mil)	-$0.60	-$0.61	-$0.63	-$0.65	-$0.67	-$2.7
Total net budget impact to DHBs ($mil)	Withheld	Withheld	Withheld	Withheld	Withheld	Withheld

Adjusted BIA for 1st March 2020 listing

Table 3 below outlines the anticipated budgetary impact from listing ivacaftor from March 1st, 2020. The 5-year NPV to the CPB is estimated to be Withheld million, with a cost of the first 12 months of Withheld million.

Table 3. Net budget impact (adjusted for 1st March 2020 listing).

	Year 1	Year 2	Year 3	Year 4	Year 5	5-YR NPV
Patient numbers	10	30	31	32	33	-
Community Pharmaceutical Budget ($mil)	Withheld	Withheld	Withheld	Withheld	Withheld	Withheld
Other DHB Costs ($mil)	-$0.20	-$0.60	-$0.62	-$0.64	-$0.66	-$2.3
Total net budget impact to DHBs ($mil)	With	With	With	With	With	Withh