Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Kalydeco

Active ingredient: Ivacaftor

Sponsor: Vertex Pharmaceuticals (Australia) Pty Ltd

November 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
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- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACFDR	Australian Cystic Fibrosis Data Registry
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomic class
BA	Bioavailability
BL	Baseline
BLQ	Below the limit of quantification
BP	Blood pressure
BMI	Body mass index
Bpm	Beats per minute
CER	Clinical evaluation report
CF	Cystic fibrosis
CFFPR	Cystic Fibrosis Foundation Patient Registry
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CI	Confidence interval
Cl^-	Chloride
CSR	Clinical study report
CV	Coefficient of variation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DILI	Drug induced liver injury
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDC	Electronic data capture

Abbreviation	Meaning
ELX	Elexacaftor
EU	European Union
F/F	Homozygous for *F508del*
F/G	Heterozygous for *F508del* and a gating mutation
F/MF	Heterozygous for *F508del* and a minimal function mutation
F/RF	Heterozygous for *F508del* and a residual function mutation
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein Food and Drug Administration
FAS	Full analysis set
FDA	Food and Drug Administration
FDC	Fixed dose combination
FE-1	Faecal elastase
FEV1	Forced expiratory volume in 1 second
FRT	Fischer rat thyroid
G551D	CFTR missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
GCP	Good Clinical Practice
geo mean	Geometric mean
GGT	Gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GLSM	Geometric least squares mean
GMR	Geometric mean ratio
H	Hour
HBE	Human bronchial epithelial
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIV-1/HIV-2 abs	Antibodies against human immunodeficiency viruses 1 and 2
HR	Heart rate
ICH	International Council for Harmonisation
IQR	Interquartile range
IRT	Immunoreactive trypsinogen
IV	Intravenous
IVA	Ivacaftor
LCI	Lung clearance index

Abbreviation	Meaning
$LCI_{2.5}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
LCI_5	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value
LFT	Liver function test
LLN	Lower limit of normal
LS	Least squares
LUM	Lumacaftor
LUM/IVA	Lumacaftor/ivacaftor
Max	Maximum value
MBW	Multiple-breath washout
MedDRA	Medical Dictionary for Regulatory Activities
MF	Minimal function (mutation)
MHI	Moderate Hepatic Impairment
Min	Minimum value
mRNA	Messenger RNA
MR	Metabolic ratio
N	Size of subsample
N	Total sample size
NA	Not applicable
NOS	Not otherwise specified
OATP	Organic anion transporting polypeptide
P	Probability
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PE	Physical examination
PEx	Pulmonary exacerbation
P-gp	P-glycoprotein
PK	Pharmacokinetic
PN	Preferred name
pp	Percentage point
ppFEV1	Percent predicted forced expiratory volume in 1 second
PR	PR interval, segment
PT	Preferred term
q12h	Every 12 hours
QD	Once daily

Abbreviation	Meaning
QRS	The portion of an ECG comprising the Q, R and S waves, together representing ventricular depolarisation
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
R117H	*CFTR* missense gene mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue
RF	Residual function
RNA	Ribonucleic acid
RR	The interval from the onset of one QRS complex to the next
RSE	Relative standard error
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SOC	System Organ Class
SOP	Standard operating procedure
SwCl	Sweat chloride
TC	Triple combination
TE	Treatment emergent
TEAE	Treatment emergent adverse event
TEZ	Tezacaftor
TEZ/IVA	Tezacaftor/ivacaftor
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WHO-DD	World Health Organisation-Drug Dictionary

Kalydeco (ivacaftor) submission

Type of submission:	Extension of indications
Product name:	Kalydeco
Active ingredient:	ivacaftor
Decision:	Approved
Date of decision:	14 February 2023
Date of entry onto ARTG:	17 February 2023
ARTG number:	198654, 198655, 267390, 269661, 342815
Black Triangle Scheme	No
Sponsor's name and address:	Vertex Pharmaceuticals (Australia), 601 Pacific Highway St Leonards NSW 2065
Dose form:	Film-coated tablets, granules.
Strength:	Film-coated tablets contain 150 mg of ivacaftor per tablet. Granules contain 25 mg, 50 mg or 75 mg of ivacaftor per sachet
Container:	Kalydeco tablets are packaged in a thermoform polychlorotrifluoroethylene [PCTFE]/foil) blister pack or a child-resistant high-density polyethylene (HDPE) bottle with a polypropylene, foil-lined induction seal closure and molecular sieve desiccant. Kalydeco granules are packaged in a Biaxially Oriented Polyethylene Terephthalate/Polyethylene/Foil/Polyethylene (BOPET/PE/Foil/PE) sachet
Pack size:	Blister pack containing 56 film-coated tablets Bottle containing 56 film-coated tablets. Granules (25mg, 50 mg and 75 mg) 56 sachets (containing 4 individual wallets with 14 sachets per wallet).
Approved therapeutic use for the current submission:	Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients aged 4 months and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay data.
Route of administration	Oral

Dosage:

Table 1: Dosing recommendations for patients aged 4 months and older with indicated mutations in at least one allele of the *CFTR* gene

Age	Weight	Dose
4 months to less than 6 months	≥5 kg	25 mg granules (one sachet) q12h
6 months and older	≥5 kg to <7 kg	25 mg granules (one sachet) q12h
	≥7 kg to <14 kg	50 mg granules (one sachet) q12h
	≥14 kg to <25 kg	75 mg granules (one sachet) q12h
	≥25 kg	150 mg tablet (one tablet) q12h

For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.

Pregnancy category:

Category B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Kalydeco (ivacaftor) background

This AusPAR describes the submission by Vertex Pharmaceuticals (Australia) (the sponsor) to register Kalydeco (ivacaftor) for the following proposed extension of indications:

> *Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients aged 4 months and older who have or at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.*

Cystic fibrosis (CF)

Cystic fibrosis is a chronic disease caused by mutations affecting the cystic fibrosis transmembrane conductor regulator (CFTR gene) that translate to abnormal functioning of the CFTR protein. The CFTR protein is a transporter for chloride across membranes and dysfunction of this protein results in abnormally viscous secretions. The CFTR protein is normally expressed in cells that produce mucous, sweat and digestive juices.

Dysfunction of the CFTR protein results in:

- Pulmonary disease: initially this presents as cough and recurrent lower respiratory tract infection, but over time progresses to bronchiectasis with progressive lung damage. This may be complicated by colonisation with *Pseudomonas*, *Staphylococcus aureus* and *Aspergillus*.
- Sinusitis and nasal polyps
- Pancreatic: exocrine insufficiency leading to malabsorption, progressing to loss of endocrine pancreatic function and diabetes
- Meconium ileus
- Hepatic: cirrhosis from biliary tract obstruction
- Infertility in males and reduced fertility in females

The most common mutation is the Δ508 mutation. The CFTR2 Website has registered 442 CFTR2 variants: 360 associated with CF, 48 of varying clinical significance, 23 non-CF-causing and 11 of unknown significance. Mutations can result in nonsense (no functional protein) or missense (dysfunctional protein) defects[1]. About 15% of mutations are not associated with disease.

In Australia, in 2020, there were 3,538 people with CF registered in the Australian Cystic Fibrosis Data Registry (ACFDR Annual Report 2020). Median age was 20.2 years and 52.8% were males. There were 47.0% homozygous for F508del and 43.0% heterozygous for F508del. Median age at death was 30.7 years. At the end of 2020, 51.7% of people in the ACFDR were taking CFTR modulators.[2]

Current treatment options for CF

The range of treatment options for CF and its complications are summarised in Table 2.

In addition, physiotherapy is used to improve and maintain lung function, and organ transplantation is used for organ failure (end-stage hepatic, pulmonary and/or cardiac failure).

The recent advances in the treatment of CF are CFTR modulators. There are three main types of CFTR modulators:

- Potentiators
- Correctors
- Amplifiers

Potentiators are drugs that can improve the function of a defective CFTR protein that is expressed at the cell surface. These drugs improve the conductance of chloride through the channel. These drugs include Kalydeco™ (IVA monotherapy), Symdeko™/Symkevi™ (TEZ/IVA), and Orkambi™ (LUM/IVA).

Correctors help a defective CFTR protein to assume the correct shape so that if can avoid degradation within the cell and instead be transported to the surface membrane.

[1] Elborn JS. Cystic fibrosis. Lancet. 2016 Nov 19;388(10059):2519-2531. doi: 10.1016/S0140-6736(16)00576-6. Epub 2016 Apr 29. PMID: 27140670.

[2] Australian Cystic Fibrosis Data Registry Annual Report 2020 https://www.cfsa.org.au/acfdr-2020-annual-report/

Amplifiers increase the production of CFTR protein by the cell. These drugs are currently in development and are not currently marketed.

IVA has efficacy for Class III and IV mutations, by restoring function to defective CFTR proteins on the cell surface membrane (potentiate). Lumacaftor, tezacaftor (TEZ) and elexacaftor (ELX) are designed for Class II mutations, to restore function to abnormal CFTR proteins allowing them to be transported to the cell surface membrane where IVA, in combination, is used to potentiate the effect.

Table 2. Treatment options for CF

CF lung disease	• Airway hydration (hypertonic saline) • Mucolytics (dornase alfa) • Oral antibiotics (amoxicillin clavulanate, ciprofloxacin, azithromycin, clarithromycin • Inhaled antibiotics (tobramycin, aztreonam, colistin) • IV antibiotics (ceftazidime, meropenem, piperacillin-tazobactam, tobramycin, amikacin) • Bronchodilators (albuterol, salmeterol) • Oxygen • Inhaled corticosteroids (budesonide, fluticasone) • Systemic corticosteroids (prednisolone, prednisone) • Chest physiotherapy
CF liver disease	• Oral bile acid therapy (ursodeoxycholic acid)
CFRD	• Insulin
CF related osteoporosis and osteopenia	• Vitamin D and calcium supplementation
Pancreatic insufficiency (PI) / malnutrition	• Pancreatic enzyme replacement • Acid reduction therapy (H2-blockers, proton-pump inhibitors) • Supplementation of fat-soluble vitamins A, D, E, and K • Appetite stimulation (hydroxyzine, cyproheptadine, megestrol acetate, dronabinol)
CF arthropathy	• Systemic corticosteroids (prednisolone, prednisone) • Methotrexate • TNF blockers, TNF receptor blockers
Anxiety and depression	• Anxiolytics • Antidepressants
Cardiac disease	• Digitalis and tolazoline hydrochloride have been reported as treatments for heart failure secondary to CF; however, no clear benefit of these treatments has been identified and they remain controversial.[24]

CF: cystic fibrosis; CFRD: cystic fibrosis related diabetes; IV: intravenous; PI: pancreatic insufficiency; TNF: tumor necrosis factor.

Clinical rationale for Kalydeco use in CF treatment

The clinical rationale to expand the indication to include Fisher rat thyroid cell line (FRT)-responsive mutations is stated by the sponsor:

> *"To enable patients with rare mutations access to CFTR modulator therapies, a paradigm was established by the FDA and Vertex which provided a pathway for adding rare mutations to the approved indications. The IVA label was expanded in 2017 to include 23 mutations indicated for the treatment of CF. TEZ/IVA was approved in 2018 for the treatment of CF in patients who carry 1 of 21 mutations. A total of 12 of the 23 mutations for IVA and 9 of the 21 mutations for TEZ/IVA were supported solely by in vitro data from the FRT system (Table 1). Reliable translation of in vitro responsiveness in the FRT system to evidence of clinical benefit across extensive development program allowed for these rare CFTR modulator-responsive mutations to be included as indicated mutations for IVA and*

TEZ/IVA. In addition, the FRT system was used to identify 10 TEZ/IVA-responsive gating mutations that were subsequently evaluated clinically."

Regulatory status

Australian regulatory status

Ivacaftor was first approved in Australia on 9 July 2013. Approval was initially for the adult population and subsequently was extended to the paediatric population, with the addition of paediatric formulations.

The current TGA approved indication for Kalydeco is:

> *Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients aged 4 months and older who have an R117H CFTR mutation (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION) or one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and Section 5.1 PHARMACODYNAMIC PROPERTIES).*

Kalydeco (ivacaftor) was granted orphan drug designation on 26 November 2021.

A similar application was recently considered for Trikafta (ELX/TEZ/IVA) to include patients with rare mutations that are responsive to Trikafta based on *in vitro* data. This indication was not supported, as a reliable prediction of clinical efficacy could not be made from the *in vitro* data.

The recently approved indication for Trikafta is:

> *Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.*

An application for Symdeko was approved in 2019. This application also included a request for rare mutations based on *in vitro* data.

The currently approved indication for Symdeko is:

> *Symdeko is indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.*

International regulatory status

As per the Section 31 response, the Kalydeco indication in the US has been expanded to include the additional ivacaftor (IVA)-responsive CFTR mutations that are currently under review with the TGA.

A similar application is under review in Israel.

The sponsor has not yet submitted a similar application in Canada. A meeting between Vertex and Health Canada to discuss the planned submission is scheduled for October 2022.

A submission is planned in New Zealand, once approval has been received in Australia.

There are no current plans to plans to submit a variation for Kalydeco to expand the label in the EU to include mutations in the CFTR gene that are responsive to IVA based on *in vitro* assay data. The CHMP have previously restricted the indication to mutations for which clinical data are available (Symkevi™ European public assessment report).[3]

Table 3. Kalydeco international regulatory status at the time of writing.

Country	Indication
Australia*	Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients aged 4 months and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and Section 5.1 PHARMACODYNAMIC PROPERTIES).
USA	Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients aged 4 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.
Europe	The approved indications for Kalydeco granules are: Kalydeco granules are indicated for the treatment of infants aged at least 4 months, toddlers and children weighing 5 kg to less than 25 kg with cystic fibrosis (CF) who have an R117H CFTR mutation or one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (see sections 4.4 and 5.1). The approved indication for Kalydeco tablets is: Kalydeco tablets are indicated: • As monotherapy for the treatment of adults, adolescents, and children aged 6 years and older and weighing 25 kg or more with cystic fibrosis (CF) who have an R117H CFTR mutation or one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (see sections 4.4 and 5.1).

[3] https://www.ema.europa.eu/en/documents/assessment-report/symkevi-epar-public-assessment-report_en.pdf

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1: Timeline for Kalydeco Submission PM-2021-05827-1-5.

Description	Date
Submission dossier accepted and first round evaluation commenced	22 December 2021
Evaluation completed	7 October 2022
delegate's[4] Overall benefit-risk assessment and request for Advisory Committee advice	3 November 2022
Advisory Committee meeting	16 December 2022
Registration decision (Outcome)	14 February 2023
Registration in the ARTG	17 February 2023
Number of working days from submission dossier acceptance to registration decision*	276

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

Quality

Quality evaluation was not required for this submission.

Nonclinical

Module 4 comprised a new *in vitro* primary pharmacology study conducted in FRT cells which was submitted in support of Trikafta.

This study examined FRT cells expressing one of 235 individual CFTR mutations, evaluated for their response to either elexacaftor/tezacaftor/ivacaftor in combination, tezacaftor/ivacaftor in combination, or ivacaftor alone. Ivacaftor alone had no effect on the processing of mutant CFTR forms. Of the mutant forms tested, chloride transport in FRT cells expressing F508del-CFTR was increased in fifty-nine mutations following treatment with ivacaftor alone, all of which are newly characterised mutations responsive to ivacaftor.

The criteria for treatment-responsiveness used in the study was a ≥10 percentage point increase in chloride transport over baseline as a percentage of normal CFTR. Free drug levels in the assay medium were not measured in the study.

[4] The 'delegate' is the delegate of the Secretary of the Department of Health and Aged Care who made the final decision to either include the new medicine/indication on the ARTG or reject the submission, under section 25 of the Therapeutic Goods Act

However, based on 3.1% unbound for ivacaftor (Study M078; Submission PM-2017-04765-1-5), the nominal *in vitro* concentration of 1 μM used for ivacaftor is consistent with the average free drug concentrations in the plasma of patients receiving Trikafta.

The non-clinical evaluator concluded that the sponsor's revised statement was generally supported by data submitted for Trikafta.

Clinical

The dossier contained a Clinical Overview, and one *in-vitro* study related to efficacy: Study P298.

The sponsor submitted a post-marketing observational study VX17-770-128 after evaluation commenced.

Efficacy

Study VX17-770-128 was a 3-year observational study evaluating the real-world clinical response using data collected by the US Cystic Fibrosis Foundation Patient Registry (CFFPR) to understand the clinical response to IVA in a subgroup of CF patients, 2 years of age and older with *CFTR* mutations that are IVA-responsive based on *in vitro* and/or clinical evidence and have a new record of IVA initiation between 17 May 2017 and 31 December 2017.

Data on clinical outcomes for at least 3 years following IVA initiation or loss of follow-up, death, or discontinuation of IVA therapy for these patients were compared annually to their respective data before IVA treatment (pre-IVA treatment period of 3 years). (see Figure 11-1, Clinical study report, Study VX17-770-128, included as an attachment for the ACM)

Results

Study VX17-770-128 included 349 patients with selected, FDA-approved ivacaftor-responsive CFTR mutations with a record of IVA initiation between 17 May and 31 December 2017.

These included 150 patients <18 years of age and 199 patients ≥18 years of age (Table 3).

Table 3. Demographic and Clinical Characteristics at IVA Initiation (copied from Table 12-1, Study VX17-770-128)

Characteristic	IVA Cohort (N = 349)
Male, n (%)	174 (49.9)
Age at index (years), Mean (SD)	27.6 (20.7)
White or Caucasian, n (%)	332 (95.1)
ppFEV$_1$[a]	
n	270
Mean (SD)	77.5 (25.4)
Mutation[b], n (%)	
A1067T	2 (0.6%)
A455E	59 (16.9%)
D110E	2 (0.6%)
D110H	2 (0.6%)
D1152H	74 (21.2%)
D1270N	13 (3.7%)
D579G	6 (1.7%)
E193K	0 (0.0%)
E56K	0 (0.0%)
F1052V	5 (1.4%)
F1074L	0 (0.0%)
G1069R	1 (0.3%)
K1060T	0 (0.0%)
L206W	41 (11.7%)
P67L	26 (7.4%)
R1070Q	1 (0.3%)
R1070W	8 (2.3%)
R117C	18 (5.2%)
R347H	32 (9.2%)
R352Q	14 (4.0%)
R74W	13 (3.7%)
S945L	41 (11.7%)
S977F	2 (0.6%)

GLI: Global Lung Function Initiative; IVA: ivacaftor; N: total sample size; n: size of subsample; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SD: standard deviation

[a] GLI equations were used to determine ppFEV$_1$. ppFEV$_1$ values are not available for patients <6 years of age as spirometry is not performed on patients below the age of 6 years.

[b] Mutation not mutually exclusive; categories may sum up to greater than 100%.

The clinical evaluator commented that all of these mutations corresponded to mutations included in Table 6 of the proposed PI. None of these mutations were in the control group for the Fischer rat thyroid (FRT) responsiveness study, and all were responsive to IVA in the FRT experiments.

According to the PI, Table 6, the following mutations did not have prior clinical data: A1067T, D110E, D110H, D1270N, E193K, E56K, F1052V, F1074L, G1069R, K1060T, R1070Q, R74W.

The following mutations did have prior clinical data: A455E (16.9% patients), D1152H (21.2%), D579G, L206W (11.7%), P67L (7.4%), R1070W, R117C (5.2%), R347H (9.2%), R352Q, S945L (11.7%), S977F. The majority of the data were therefore from mutations that had some prior clinical data.

The data source was the US Cystic Fibrosis Foundation Patient Registry (CFFPR). Outcomes data were compared for the 3 years after initiation of IVA with the 3 years prior to the initiation.

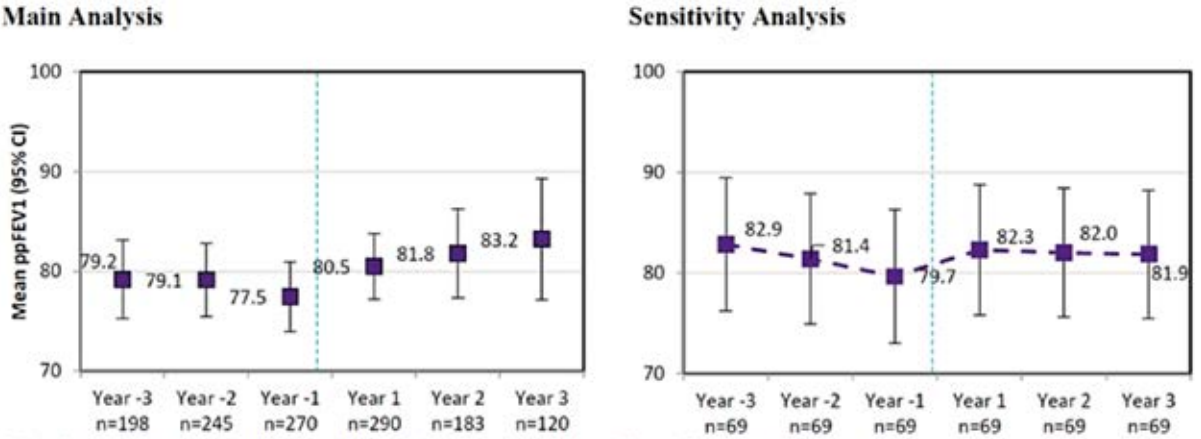
Study endpoints included lung function measurements (percent predicted forced expiratory volume in 1 second [ppFEV1]), pulmonary exacerbations, hospitalisations, nutritional parameters (weight, BMI, and z-scores for weight and BMI), death, organ transplantation, selected CF complications, and selected pulmonary microorganisms.

Of the 349 patients entering the cohort, 167 (47.9%) remained in the cohort at the end of the third year of follow-up. The main reasons for discontinuing were the initiation of another CFTR modulator, 162 (46.4%) patients, or the discontinuation of IVA, 66 (18.9%) patients.

Mean (SD) baseline ppFEV1 was 77.5 (25.4) %. Mean (SD) duration of exposure was 21.19 (12.36) months and 168 (48.1%) patients were treated for >24 to ≤36 months.

The main analysis showed an improvement in ppFEV1 over the three years of treatment. A sensitivity analysis was performed in a subset of patients with no missing observations also indicated an improvement from baseline.

Observed ppFEV1 Over Time Among Patients ≥6 Years of Age, Main Analysis and Sensitivity Analysis (copied from Figure 12-2, Study VX17-770-128)



IVA: ivacaftor; n: size of subsample; $ppFEV_1$: percent predicted forced expiratory volume in 1 second
Note: The dotted line indicates the initiation of IVA treatment. Mean values for each 12-month interval are presented with corresponding standard errors. If patients had more than 1 encounter in the interval, all patient data within the interval were averaged.

The absolute change from pre-baseline to Year 3 was 1.7 (0.2 to 3.2) %. The clinical evaluator highlighted that there were too few subjects in each of the individual subgroups of mutations to infer meaningful conclusions. Of the mutations without prior clinical data, analyses were performed for R74W and D1270N which showed improvement in the first year of treatment but not in years 2 and 3. It is further noted that for the absolute change from pre-baseline to Year 3, confidence intervals were wide for a number of mutations in Year 3 (Table 4).

Table 4. Absolute Change in ppFEV1 From Pre-treatment Baseline, Individual Mutation Subgroup Analysis (copied from Table 12-5, Study VX17-770-128)

CFTR Mutation	Pre-treatment baseline	Absolute change from baseline to: Year 1	Year 2	Year 3
D1152H				
n	58	58	35	15
Mean (95% CI)	81.0 (75.0, 86.9)	+1.2 (-0.4, 2.8)	+1.3 (-0.7, 3.4)	+2.4 (-1.3, 6.2)
A455E				
n	49	48	27	19
Mean (95% CI)	68.7 (61.5, 76.0)	+2.8 (0.5, 5.1)	+2.4 (-0.5, 5.2)	+2.7 (-0.7, 6.0)
S945L				
n	38	38	23	17
Mean (95% CI)	75.5 (67.4, 83.7)	+3.1 (1.5, 4.7)	+3.2 (-0.2, 6.5)	+1.7 (-3.2, 6.6)
R347H				
n	25	25	14	13
Mean (95% CI)	75.0 (63.0, 87.1)	+5.1 (3.2, 7.1)	+7.1 (3.2, 11.0)	+4.6 (1.3, 7.9)
L206W				
n	25	25	16	7
Mean (95% CI)	88.4 (77.9, 98.8)	+1.8 (-0.5, 4.1)	-0.7 (-4.5, 3.1)	-0.8 (-6.8, 5.2)
P67L				
n	23	22	14	9
Mean (95% CI)	76.6 (65.4, 87.7)	+4.5 (1.7, 7.2)	+1.6 (-2.6, 5.7)	+0.2 (-5.6, 6.0)
R74W				
n	12	12	8	7
Mean (95% CI)	86.3 (67.9, 104.7)	+0.6 (-3.7, 4.9)	-2.1 (-9.7, 5.6)	-0.7 (-9.0, 7.7)
D1270N				
n	11	11	7	5
Mean (95% CI)	72.0 (51.2, 92.9)	+2.2 (-2.2, 6.5)	-1.6 (-10.9, 7.8)	-1.2 (-17.7, 15.3)

The proportion of patients with pulmonary exacerbations decreased with treatment. BMI z scores improved over the three years in the ≥2 to <20 years age group and BMI increased in the >18 years age group.

Over the 3-year study period, there were a total of 2 deaths (0.6%) in the IVA cohort. Both deaths were adult patients.

The clinical evaluator concluded that overall, these results support improvements in lung function, decreased hospital admissions and improvements in nutrition parameters. Previous clinical trial data have demonstrated efficacy for the G552D, F508del and R117H mutations. In addition, Study VX12-770-111, KONNECTION provided efficacy data for the following mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D.

Safety

There were no clinical safety data in the dossier.

Risk Management Plan (RMP) evaluation

RMP evaluation was not required for this submission.

Discussion

The submitted data are potentially sufficient for registration, taking into consideration the non-clinical and clinical evaluations for this application. The non-clinical evaluation has established

that the nominal *in vitro* concentration used for ivacaftor is consistent with the average free drug concentrations in the plasma of patients, based on the evaluation of studies P298 and M078. Acknowledging that the *in vitro* Fischer rat thyroid assay data is not a predictor for clinical efficacy but identifies potentially responsive mutations, the sponsor has agreed to remove this statement from the proposed product information for Kalydeco.

The post-marketing study VX17-770-128 provides some evidence of overall improvements in clinically relevant outcomes and correlation with *in vitro* data, while acknowledging that there were few subjects in each of the individual subgroups of mutations to infer meaningful conclusions and a considerable attrition rate of patients by the end of year 3.

ACM advice is requested, in view of the inclusion of the 4 months and older age group in the proposed indication, given the lack of data in infants and the extrapolation of data from other age groups to this group. The post-marketing study VX17-770-128 included children aged 2 years and older and the applicability of this study to younger patients is unclear.

Discussion is warranted, in light of the previous similar applications for Trikafta and Symdeko, noting the FDA's position in establishing efficacy using in vitro data in lieu of a clinical trial for the CFTR modulators including ivacaftor[5], and the approach of the EU in restricting the indication for CFTR modulators to mutations for which clinical data is available. It is noteworthy that the EMA has also expressed concerns with the Fischer rat thyroid assay data and its limitations in predicting clinical efficacy.[3]

Conclusions

The submitted data are potentially sufficient for registration. A final decision will be made regarding the wording of the proposed indication, following ACM.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the delegate's overview, as well as the sponsor's response to these documents, advised the following.

1. ***What is the view of the ACM on the indication proposed by the sponsor, taking into consideration the TGA evaluations and the submitted post-marketing observational study? Please also comment on the inclusion of the 4 months and older age group in the proposed indication, given the lack of data in infants.***

The ACM was of the view that the post-marketing observational data for ivacaftor is reassuring.

The ACM noted that cystic fibrosis is an inherited progressive disease that produces symptoms from early age and agreed that early interventive therapies would be beneficial to CF patients. The ACM considered that ivacaftor has a positive risk benefit profile for the treatment of CF in patients aged 4 months and older age group. The ACM further noted that some forms of CF are active at birth and reiterated that early access to effective treatment is important.

2. ***Does the ACM have further comments on the proposed indication for Kalydeco, considering the Australian, US and EU regulatory status of similar applications, including Symdeko and Trikafta, in regard to rare mutations that are responsive based on in vitro data?***

[5] Ann Am Thorac Soc Vol 15, No 1, pp 1–2, Jan 2018

The ACM noted that the proposed indication is consistent with the approved indication in the USA. The ACM considered that the submitted data from clinical and FRT assay studies were sufficient to demonstrate efficacy of ivacaftor in the proposed indication.

The ACM advised that the proposed indication for Kalydeco is acceptable.

The ACM noted that in clinical practice, care would be provided by a multi-disciplinary team and include genetic testing to determine the gene mutation/deletion that individual CF patients possess. This information is critical for determining the most appropriate treatment. The ACM noted that treatment will be based on FRT assay data and/or clinical data from the registry. Hence, the ACM advised that the list of mutation responsive ivacaftor should be included in the PI to support the clinician prescribing ivacaftor.

3. The ACM is also requested to provide advice on any other issues that it thinks may be relevant.

The ACM noted that weight gain is commonly seen with the use of CFTR modulators. Patients on these modulators should have their dietary intake assessed by dietitians with specific consideration as to whether the historic high fat CF diet is still applicable for each patient. Considering this, the ACM advised that the Product Information (PI) and Consumer Medical Information (CMI) should include a recommendation to see a dietitian for advice on high fat diets.

The ACM also noted that the information on high fat diets within the PI and CMI is vague and recommended that additional clarification on a high fat meal be included. The ACM's proposed wording is 'ivacaftor should be taken with a meal with a minimum of 8 grams of fat'. The ACM also noted that this statement should be included across the class of CFTR modulators.

The ACM was unable to identify any evidence / data suggesting upper respiratory tract infection as a common side effect of ivacaftor and advised that it should be removed from the CMI and PI. The ACM advised that upper airway congestion is not uncommon with highly effective modulators (HEMs) and queried whether this was misclassified as upper respiratory tract infections.

The ACM also advised that the wording in the CMI, 'If you experience significant pain or discomfort in the upper right stomach (abdominal) area' was unsatisfactory and needed to be re-phrased.

The ACM noted that criterion for success in the FRT assay was a 10% net increase in *in vitro* chloride transport over baseline when expressed as a percentage of normal CFTR chloride transport. This was chosen because 10% of normal CFTR function is associated with less severe disease progression and has been predictive of clinical response. The ACM acknowledged that the statement on the predictive potential of the FRT assay in Section 5.1 of the PI is acceptable in this submission due to the supportive clinical data and biological relevance for gating mutations.

The ACM discussed the usage of FRT assay as part of registration applications and advised that it would be appropriate to consider each application on its particular / individual merit. The ACM also highlighted that clinical efficacy data remains important however decisions will be made on the totality of evidence.

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients aged 4 months and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor*

potentiation based on clinical and/or in vitro assay data. (*see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and Section 5.1 PHARMACODYNAMIC PROPERTIES).*

Outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Kalydeco (ivacaftor) for the following extension of indications:

Kalydeco is indicated for the treatment of cystic fibrosis (CF) in patients aged 4 months and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data(see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and Section 5.1 PHARMACODYNAMIC PROPERTIES)

Attachment 1. Product Information

The Product Information (PI) approved with the submission for Kalydeco which is described in this AusPAR can be found as Attachment 1. It may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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