Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Dapagliflozin

Proprietary Product Name: Forxiga

Sponsor: AstraZeneca Pty Ltd

April 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An 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.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACE-I	Angiotensin converting enzyme inhibitor
ACM	Advisory Committee on Medicines
ACT	Australian Capital Territory
AE	Adverse event
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific Annex
BNP	B-type natriuretic peptide
BSA	Body surface area
CI	Confidence interval
CMI	Consumer Medicines Information
CV	Cardiovascular
DAE	Discontinuation of study drug due to adverse event
DKA	Diabetic ketoacidosis
DLP	Data lock point
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency (European Union)
EU	European Union
FDA	Food and Drug Administration (United States)
HR	Hazard ratio
IQR	Interquartile range
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire total symptom score

Abbreviation	Meaning
NNT	Number needed to treat
NSW	New South Wales
NT pro BNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PI	Product Information
PSUR	Periodic safety update report
PT	Preferred Term
PY	Patient years
RMP	Risk management plan
SAE	Serious adverse event
SD	Standard deviation
SGLT2	Sodium glucose co-transporter 2
SOC	System Organ Class
T2DM	Type 2 diabetes mellitus
US(A)	United States (of America)

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Product name:	Forxiga
Active ingredient:	Dapagliflozin (as propanediol monohydrate)
Decision:	Approved
Date of decision:	4 November 2020
Date of entry onto ARTG:	5 November 2020
ARTG number:	180147
, *Black Triangle Scheme:*[1]	No
Sponsor's name and address:	AstraZeneca Pty Ltd 66 Talavera Road Macquarie Park, NSW, 2113
Dose form:	Film coated tablet
Strength:	10 mg
Container:	Blister pack
Pack sizes:	7 tablets; 28 tablets
Approved therapeutic use:	***Heart failure*** *Forxiga is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fraction, as an adjunct to standard of care therapy (see section 5.1 Pharmacodynamic properties).*
Route of administration:	Oral
Dosage:	The recommended dose of Forxiga is 10 mg taken orally once daily at any time of the day regardless of meals. Forxiga should be used in conjunction with individualised standard of care therapy. For further information regarding dosage, refer to the Product Information.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This 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..

Product background

This AusPAR describes the application by AstraZeneca Pty Ltd (the sponsor) to register Forxiga (dapagliflozin, as propanediol monohydrate) 10 mg film-coated tablets, for the following proposed extension of indications:

> *Forxiga is indicated in adults for the treatment of heart failure with reduced ejection fraction.*

Heart failure is a clinical syndrome that presents with typical signs and symptoms reflecting the inability of the heart to fill with blood at normal pressure or to eject sufficient blood to supply the organs of the body. The most frequent symptom, which is common to a wide range of diseases not just affecting the heart, is breathlessness on exertion. As the disease progresses, breathlessness may develop on lying down, bending forward, and at rest, and be accompanied by other non-specific symptoms such as fatigue and ankle swelling. A range of conditions that affect the structure or function of the heart may trigger heart failure and researchers and clinicians have used a number of different approaches to classify and define both the syndrome and the potential causes.[2]
Heart failure is estimated to affect over 38 million people worldwide and about 480,000 people in Australia. It is more common among the elderly and has a significantly greater prevalence in the indigenous Australian population.[3] Between 2015 and 2016, there were about 173,000 hospitalisations in Australia where heart failure and cardiomyopathy were recorded as the main or additional diagnosis, representing 1.6% of all hospitalisations.[4] In the New South Wales (NSW) and Australian Capital Territory (ACT) SNAPSHOT study of patients hospitalised with heart failure over one month in 2013, the median length of stay was six days and 58% were categorised as heart failure with reduced ejection fraction.[5]

According to the National Heart Foundation of Australia, and the Cardiac Society of Australia and New Zealand's clinical guidelines for the management of heart failure, the syndrome is commonly classified into two categories (as summarised in Table 1, below)

[2] The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure European Heart Journal 37:2129-200
[3] Atherton JJ, Audehm R, Connell C (2019) Heart failure guidelines. A concise summary for the GP Medicine Today 20:14-24
[4] Australian Institute of Health and Welfare. Admitted patient care 2015–16: Australian hospital statistics. Canberra: AIHW; 2017.
[5] Newton PJ, Davidson PM, Reid CM, et al. Acute heart failure admissions in New South Wales and the Australian Capital Territory: the NSW HF Snapshot Study. Med J Aust. 2016;204(3):113.e1-113.e1138.

based on the left ventricular ejection fraction and other objective evidence of failure, along with the presence of symptoms with or without clinical signs of heart failure.[6]

Table 1: Diagnostic criteria for heart failure

Classification	Diagnostic criteria
Heart failure with reduced ejection fraction	• Symptoms with or without signs of heart failure; and • left ventricular ejection fraction < 50%[a]
Heart failure with preserved ejection fraction	• Symptoms with or without signs of heart failure; and • left ventricular ejection fraction ≥ 50%; and • objective evidence of: – relevant structural heart disease (left ventricular hypertrophy, left atrial enlargement); and/or – diastolic dysfunction, with high filling pressure demonstrated by any of the following: § invasive means (cardiac catheterisation) § echocardiography § biomarker (elevated BNP or NT proBNP) § exercise (invasive or echocardiography)

BNP: B-type natriuretic peptide, NT: N-terminal.

a) If left ventricular ejection fraction is mildly reduced (in the range of 41 to 49%), additional criteria are required (for example, signs of heart failure; diastolic dysfunction with high filling pressure demonstrated by invasive means or echocardiography or biomarker testing).

Symptomatic patients with or without signs of heart failure, who are found to have a left ventricular ejection fraction < 50%, are classified as having heart failure with reduced ejection fraction. Those patients experiencing symptoms with or without signs of heart failure where the left ventricular ejection fraction is ≥ 50% require additional objective evidence to confirm a diagnosis of heart failure with preserved ejection fraction. This evidence frequently is provided by echocardiography but depending on the underlying cause of the symptoms, may require alternative diagnostic testing. Most research to date has reported reduced mortality and morbidity in response to new therapies in the heart failure with reduced ejection fraction group, with less evidence of efficacy among patients with preserved ejection fraction.

International guidelines include a third category, heart failure with mid-range ejection fraction, where the left ventricular ejection fraction ranges between 40% and 49%.[2] This definition is likely to be more relevant for research purposes. It shares features with both heart failure with reduced ejection fraction, and preserved ejection fraction.

The New York Heart Association (NYHA) criteria categorise heart failure into four classes based on patient symptoms and function, as shown in Table 2 below.[7] Class I describes an

[6] NHFA CSANZ Heart Failure Guidelines Working Group (2018) National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018 Heart, Lung and Circulation 27:1123-1208

[7] Criteria Committee, New York Heart Association , Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

asymptomatic cohort that does not appear to satisfy the definitions of either heart failure with reduced or preserved ejection fraction.

Table 2: New York Heart Association Functional Classification of heart failure

Classification	Criteria
Class I	No limitation of ordinary physical activity
Class II	Slight limitation of ordinary physical activity No symptoms at rest
Class III	Marked limitation of ordinary physical activity No symptoms at rest
Class IV	Symptoms on any physical activity or at rest

Australian and International guidelines regarding the optimal treatment of heart failure (after addressing any underlying preventable or treatable cause of the syndrome) agree that the initial management of heart failure with reduced ejection fraction should include angiotensin converting enzyme inhibitors (ACE-I) if tolerated, otherwise substituted for angiotensin II receptor blockers (ARB), beta blockers and low-dose mineralocorticoid receptor agonists, to improve survival and decrease hospitalisations for heart failure. Additional therapies, depending on the patient and the contributing pathology, may include diuretics, ivabradine, or change from ACE-I/ARB to an angiotensin receptor neprilysin inhibitor, for example sacubitril-valsartan. Patients with heart failure with preserved ejection fraction may be adequately treated with diuretics and management of hypertension if present; patients with valvular, pericardial or congenital heart disease may benefit from a surgical intervention, including implanted electronic devices. A multidisciplinary approach that involves physiotherapy, exercise interventions, dietitians, psychologists and heart failure nurses may also improve survival and decrease re-hospitalisations.

More recently, some sodium glucose co-transporter 2 (SGLT2) inhibitors have shown improved outcomes in patients with heart failure and type 2 diabetes mellitus (T2DM). Among those, dapagliflozin is a selective competitive SGLT2 inhibitor that was first approved in Australia in 2012 as a treatment for T2DM, based on its glucuretic properties. More recent research (from the DECLARE-TIMI 58 trial) reported that dapagliflozin can reduce the risk of hospitalisation for heart failure in adults with T2DM together with established cardiovascular disease or with risk factors for cardiovascular disease.[8]

Dapagliflozin is a reversible inhibitor of SGLT2, a receptor selectively expressed in the proximal convoluted tubules in the kidney. SGLT2 is the major transporter for glucose reabsorption in the kidney. The inhibition of renal glucose reabsorption results in increased glucose excretion in the urine (glycosuria). SGLT2 inhibitors also promote renal sodium excretion (natriuresis) and activate tubule-glomerular feedback. This leads to a reduced transcapillary pressure gradient and reduced albumin excretion by the kidney. The diuretic effect of glycosuria and natriuresis causes a reduction in plasma volume, decreased cardiac pre-load and wall stress.

[8] Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-357.

Regulatory status

Australian regulatory status

Dapagliflozin received initial registration on the Australian Register of Therapeutic Goods (ARTG) in October 2012 to improve glycaemic control in type 2 diabetes mellitus with the following indication:

> ***Monotherapy***
>
> *Dapagliflozin is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated.*
>
> ***Initial combination***
>
> *Dapagliflozin is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control in patients with type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycaemic control and there are poor prospects for response to metformin monotherapy (for example, high initial HbA1c levels).*
>
> ***Add-on combination***
>
> *Dapagliflozin is indicated in patients with type 2 diabetes mellitus to improve glycaemic control:*
>
> *in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycaemic control;*
>
> *in combination with a sulfonylurea (SU), when a SU alone with diet and exercise does not provide adequate glycaemic control;*
>
> *in combination with insulin (alone or with one or both of metformin or a sulfonylurea [SU]) when the existing therapy, along with diet and exercise, does not provide adequate glycaemic control.*

The current indication to improve glycaemic control in adults with type 2 diabetes mellitus is as follows:

> ***Type 2 diabetes mellitus - Glycaemic control:***
>
> *Forxiga is indicated in adults with type 2 diabetes mellitus as monotherapy as an adjunct to diet and exercise in patients for whom metformin is otherwise indicated but was not tolerated; as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control when diet and exercise have failed to provide adequate glycaemic control and there are poor prospects for response to metformin monotherapy (for example, high initial haemoglobin A1c [HbA1c] levels); in combination with other anti-hyperglycaemic agents to improve glycaemic control, when these together with diet and exercise, do not provide adequate glycaemic control (see section 5.1 Pharmacodynamic properties - Clinical trials and section 4.4 Special warnings and precautions for use for available data on different add-on combination therapies).*

In April 2020 dapagliflozin was approved for use in the prevention of hospitalisation for heart failure in adults with type 2 diabetes mellitus with the following indication:

> ***Type 2 diabetes mellitus - Prevention of hospitalisation for heart failure:***
>
> *Forxiga is indicated in adults with type 2 diabetes mellitus and established cardiovascular disease or risk factors for cardiovascular disease to reduce the risk of*

hospitalization for heart failure (see section 5.1 Pharmacodynamic properties - Clinical trials).

International regulatory status

Dapagliflozin was submitted to the European Medicines Agency (EMA) in November 2019 and is under evaluation for use in the European Union (EU) for the following proposed indication:

Forxiga is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

Dapagliflozin was submitted to Health Canada in December 2019 and approved in June 2020 with the following indication:

Forxiga is indicated in adults, as an adjunct to standard of care therapy, for the treatment of heart failure with reduced ejection fraction (HFrEF) to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit.

Under the trade name Farxiga, dapagliflozin was submitted to the United States (US) Food and Drug Administration (FDA) in November 2019 and approved in May 2020 for use in heart failure with the following indication:

To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV).

Similar applications have been submitted in Singapore (submitted: 30 October 2019; approved: 7 July 2020), Switzerland (submitted: 27 January 2020; approved: 2 July 2020) and New Zealand (submitted: 19 February 2020; under evaluation).

The sponsor stated that there are no significant differences between the data in the Australian submission and the data packages submitted in the EU, the USA and Singapore.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 3: Timeline for Submission PM-2019-05370-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	18 December 2019
First round evaluation completed	29 May 2020
Sponsor provides responses on questions raised in first round evaluation	25 June 2020

Description	Date
Second round evaluation completed	4 August 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	27 August 2020
Sponsor's pre-Advisory Committee response	15 September 2020
Advisory Committee meeting	2 October 2020
Registration decision (Outcome)	4 November 2020
Completion of administrative activities and registration on the ARTG	5 November 2020
Number of working days from submission dossier acceptance to registration decision*	200 days

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The submitted nonclinical data package consisted of one *in vitro* and two *in vivo* primary pharmacology studies. The *in vivo* studies investigated the efficacy and/or potential mechanism of action of dapagliflozin in pre-diabetic and diabetic mouse models that exhibit features of heart failure with reduced, and with preserved ejection fraction. The study experimental designs, number of animals used, and the dosing routes (oral: drinking water or food) were appropriate. In the absence of direct pharmacokinetic measurements, the doses used in these studies (1 to 4 mg/kg) ranged from approximately one to four times the anticipated clinical exposure at the maximum recommended human dose, on a body surface area (BSA)-adjusted basis.

Overall, the submitted nonclinical primary pharmacology data showed cardioprotective effects of dapagliflozin in *in vivo* mouse models of heart failure, and suggested a mechanism involving the attenuation of the NLRP3 inflammasome,[9] (with involvement of AMP-activated protein kinase (AMPK) phosphorylation). These properties support the potential utility of dapagliflozin in the amelioration of heart failure with reduced ejection fraction, and possibly heart failure with preserved ejection fraction.

[9] NLRP3 = NLR family pyrin domain containing protein 3.

Clinical

The TGA has adopted the following EU guideline regarding heart failure:

- Note for guidance on clinical investigational of medicinal products for the treatment of cardiac failure (CPMP/EWP/235/95, Rev.1; 16 December 1999).

This guidance document indicates that the most important objectives in the treatment of heart failure are improvements in symptoms, cardiovascular morbidity and mortality. Primary endpoints for the purposes of regulatory approval of drugs to treat chronic HF are stated to be clinical symptoms, cardiovascular morbidity and all-cause mortality, and secondary endpoints are stated to be quality of life, exercise capacity, physical symptoms, haemodynamic changes (for example, ejection fraction), renal function and neurohumoral variables. The document states that whatever the endpoints selected, it must be shown that the drug does not have adverse effects on morbidity or survival.

The sponsor has also referred to the following guidances not formally adopted by the TGA:

- European Union (EMA): Guideline on clinical investigational medicinal products for the treatment of chronic heart failure (CPMP/EWP/235/95, Rev.2; 20 July 2017); and
- United States (FDA): Treatment for Heart Failure: Endpoints for Drug Development (June 2019).

Pharmacology

Pharmacokinetics

No new pharmacokinetic data were submitted.

Population pharmacokinetic data

No population pharmacokinetic data were submitted.

Pharmacodynamics

No new pharmacodynamic data were submitted.

The dapagliflozin dose selected for the pivotal study for the treatment of heart failure was based on evidence that the 10 mg daily dose that is marketed for the treatment of T2DM and for the prevention of cardiovascular events in patients with T2DM is well tolerated and effective. The sponsor states that 10 mg daily is expected to near maximally inhibit SGLT2 in the kidney.

Efficacy

The follow study was evaluated for efficacy:

- *Study D1699C00001*: a study to evaluate the effect of dapagliflozin on the incidence of worsening heart failure or cardiovascular death in patients with chronic heart failure with reduced ejection fraction (also known as the Dapagliflozin And Prevention of Adverse outcomes in Heart Failure; or the DAPA-HF trial).

This study is a multinational, multicentre, event-driven, randomised, double-blind, placebo-controlled Phase III trial in 4744 adult patients with chronic heart failure with reduced ejection fraction. The study compared the effect of dapagliflozin 10 mg once daily in addition to regional standard of care therapies for heart failure to placebo in addition to standard of care on the occurrence of cardiovascular (CV) death, hospitalisation for heart failure or urgent heart failure visit, patient reported outcomes and renal outcomes.

After a baseline enrolment visit at Day -14, patients were randomised on Day 0 at a ratio of 1:1 to 10 mg dapagliflozin or placebo (placebo) arms. Patient recruitment was

continuously monitored and randomisation stratified for T2DM status. In addition to T2DM status, randomisation was also monitored for geographic region, left ventricular ejection fraction value, NYHA class and atrial fibrillation status.

Key inclusion criteria for participants were a documented diagnosis of NYHA Class II to IV heart failure with reduced ejection fraction which had been present for at least two months and was optimally treated; left ventricular ejection fraction ≤ 40% within the last 12 months prior to enrolment and at least three months after any surgical or pharmacological intervention for heart failure (left ventricular function was re-assessed at the enrolment visit if no assessment had been done within 12 months, or if results of prior assessments within 12 months were not available); N-terminal pro b-type natriuretic peptide (NT-proBNP) ≥ 600 pg/mL at enrolment (≥ 400 pg/mL if the patient had been hospitalised for heart failure within the last 12 months) and estimated glomerular filtration rate (eGFR) ≥ 30mL/min/1.73m^2. Optimal treatment of heart failure was considered to include (unless contraindicated or not tolerated) an ACE-I or ARB or ARNI plus a beta-blocker plus a mineralocorticoid receptor antagonist (if appropriate according to treating physician). Key exclusion criteria included recent treatment with an SGLT2 inhibitor or intolerance to SGLT2 inhibitor, type 1 diabetes mellitus, symptomatic hypotension, acute decompensated heart failure, major CV event in the preceding 12 weeks, cardiac surgery or device implantation in the preceding 12 weeks, heart failure due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic obstructive cardiomyopathy, uncorrected primary valvular disease; symptomatic bradycardia, or second or third degree heart block (without pacemaker), and a number of protocol specified conditions with regard to hepatic function, infections, malignancy and pregnancy.

The first patient was enrolled on 8 February 2017 and the last patient visit was on 17 July 2019. The analyses were based on a database lock date of 11 August 2019. In total, 4744 patients were randomised (2373 to dapagliflozin and 2371 to placebo) and 4710 (99.3%) patients had complete follow-up of the primary endpoint (dapagliflozin, n = 2359 (99.4%); placebo, n = 2351 (99.2%)). Nine patients withdrew consent and the vital status was known for all nine participants. Two participants were lost to follow-up (that is, vital status unknown). Disposition was comparable for participants in the two treatment groups. Overall, the median follow-up time until the primary analysis censoring date was 18.2 months (range: 0, 27.8 months).

The primary efficacy variable was time to the first occurrence of a composite endpoint of CV death or heart failure event (hospitalisation for heart failure or urgent heart failure visit.

The secondary efficacy variables in hierarchical order were:

- time to first occurrence of CV death;
- time to first occurrence of hospitalisation for heart failure;
- total number of heart failure hospitalisations (initial and recurrent) and CV death;
- Change from Baseline measured at 8 months in the total symptom score of the KCCQ, a specific heart failure patient reported outcome questionnaire [10]
- time to first occurrence of a composite endpoint of sustained decline in eGFR of ≥ 50%, end-stage renal disease; or renal death; and
- time to death from any cause.

[10] Green CP, Porter CB, Bresnahan DR, Spertus JA, Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol, 35:1245-5 (2000).

The analysis of the primary efficacy endpoint used a Cox proportional hazards model with a factor for treatment group, stratified by T2DM status at randomisation, and adjusted for history of hospitalisation for heart failure. Kaplan-Meier estimates of the cumulative proportion of patients with heart failure events were calculated and plotted by treatment group. The analysis considered withdrawal of consent, non-CV death, date of last clinical event assessment and primary analysis censoring date as censoring dates without a primary event. The study was event-driven with 844 pre-determined adjudicated primary endpoints required to give the study 90% power to demonstrate superiority of dapagliflozin relative to placebo with a hazard ratio (HR) of 0.80. With an assumed annual event rate of 11% in the placebo group, 4500 patients were estimated to provide the required number of primary events, based on an anticipated recruitment period of 18 months and an average follow-up period of approximately 24 months. An interim analysis was carried out by an independent data monitoring committee when approximately 75% of the primary events had been adjudicated. The sponsor and investigators remained blinded to the results of the interim analysis.

Sensitivity analyses included analyses where 'undetermined' deaths were treated as censoring events, and a 'worst case scenario' analysis where all cases censored before the primary analysis censoring date for any reason in the dapagliflozin arm, but not in the placebo arm, were treated as having experienced a primary event at the time of censoring.

Descriptive exploratory sub-group analyses of the primary composite endpoint and CV death were presented by T2DM status and history of heart failure hospitalisation. The composite outcome of recurrent heart failure hospitalisations (that is, first and recurrent) or CV death was analysed using a semi-parametric proportional rates model to test for treatment effect and to quantify the treatment difference in terms of the rate ratio with 95% confidence interval and p-value. Group-level comparisons of change in KCCQ total symptom score (KCCQ-TSS) from Baseline to 8 months were conducted using a rank-ANCOVA and the win ratio to test the null hypothesis of no differences in the distributions of ranked outcomes between the two treatment arms. The number and percentage of patients achieving a clinically meaningful change from baseline (increase or decrease of score ≥ 5 points) in the KCCQ-TSS in each treatment group were also analysed using logistic regression models.

The demographic characteristics were well balanced between the two treatment groups. The mean (standard deviation; SD) age of the total population was 66.3 (10.9) years, with 57.2% of the population aged > 65 years, 76.6% male, 70.3% White, 23.5% Asian, and 4.8% Black or African American. The mean body mass index (BMI) (SD) in the total population was 28.2 (6.0) kg/m^2, with 35.3% of the total population having a BMI ≥ 30 kg/m^2. Baseline disease characteristics were also balanced between the two groups. A similar proportion of patients in each arm had T2DM at Baseline (dapagliflozin 45.3%, placebo 44.9%). At enrolment, most patients were classified as NYHA Class II (67.5%, dapagliflozin 67.7%, placebo 67.4%), 31.6% as NYHA Class III (dapagliflozin 31.5%, placebo 31.7%) and 0.9% as NYHA Class IV (dapagliflozin 0.8%, placebo 1.0%). In the total population the median (interquartile range; IQR) left ventricular ejection fraction was 32% (26%, 37%). The most common heart failure with reduced ejection fraction aetiology was ischaemic heart disease (56.4% of patients). In the total population, the median (IQR) NT-proBNP levels were 1437 pg/mL (857, 2650). Heart failure treatment at randomisation was balanced between the two treatment groups. In the total group, 93.6% were being treated with an ACE-I/ARB/ARNI, 96.1% with a beta blocker, 71.0% with an mineralocorticoid receptor antagonist, and 93.4% with a diuretic, most commonly a loop diuretic.

Dapagliflozin was superior to placebo in reducing the incidence of the primary composite endpoint of CV death or a heart failure event: hazard ratio (HR) 0.74, 95% confidence interval (CI): 0.65, 0.85, p < 0.0001. In the dapagliflozin arm 386 (16.3%) patients experienced an event compared to 502 (21.2%) patients in the placebo arm. This

corresponded with 11.6 events / 100 patient years (PY) of follow-up in the dapagliflozin group and 15.6 in the placebo group (see Table 4, below). The annualised number needed to treat (NNT) for the primary composite endpoint was 26 patients (95% CI: 18, 46).

Table 4: DAPA-HF trial Results for the primary composite end point

Endpoint	Dapagliflozin 10 mg (n = 2373)		Placebo (n = 2371)		Results (dapagliflozin/placebo)		
	n (%)	ER	n (%)	ER	HR	95% CI	p-value
CV death / hospital for HF / urgent HF visit	386 (16.3)	11.6	502 (21.2)	15.6	0.74	0.65, 0.85	< 0.0001
CV death / hospital for HF	382 (16.1)	11.4	495 (20.9)	15.3	0.75	0.65, 0.85	< 0.0001
CV death	227 (9.6)	6.5	273 (11.5)	7.9	0.82	0.69, 0.98	0.0294
Hospital for HF / urgent HF visit	237 (10.0)	7.1	326 (13.7)	10.1	0.70	0.59, 0.83	< 0.0001
Hospital for HF	231 (9.7)	6.9	318 (13.4)	9.8	0.70	0.59, 0.83	< 0.0001
Urgent HF visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43	0.20, 0.90	0.0213

CV = cardiovascular; HF = heart failure; n = number of subjects; ER = event rate; HR = hazard ratio; CI = confidence interval.

Source: Adapted from the clinical study report, Table 14.2.2.1. The number of events for the individual components are the actual number of first events for each component and their sum exceeds the number of events for the composite endpoint. Event rates are presented as the number of subjects with event per 100 patient years of follow-up. Hazard ratio for dapagliflozin 10 mg versus placebo, 95% confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model (score test) stratified by T2DM status at randomisation, with factors for treatment group and history of HF hospitalisation.

Each of the three components of the primary composite endpoint individually contributed to the overall treatment effect. Treatment with dapagliflozin was associated with an 18% (95% CI: 2%, 31%) reduction in the risk of CV death relative to placebo, a 30% (95% CI: 17%, 41%) reduction in the risk of hospitalisation for heart failure relative to placebo, and a 57% (95% CI: 10%, 80%) reduction in the risk of urgent heart failure visits relative to placebo. Sensitivity analyses were consistent with the primary analyses. The Kaplan-Meier curves for dapagliflozin and placebo diverged early in treatment and continued to separate over time.

The superiority of dapagliflozin on the composite of CV death, hospitalisation for heart failure or urgent heart failure visit was generally consistent across sub-groups. Of particular note, the results for the sub-group analyses in heart failure with reduced ejection fraction patients with T2DM or without TD2M were similar. However, the subgroup analysis of the composite primary efficacy endpoint by NYHA Class (Class II versus Class III and IV combined) indicated that dapagliflozin was more effective than placebo only in patients with NYHA Class II heart failure (HR 0.63, 95% CI 0.52, 0.75) and not in the combined NYHA Class III and IV patients (HR 0.90, 95% CI 0.74, 1.09). In a response to a TGA request for information, the sponsor provided additional *post hoc* analyses of the primary endpoint by NYHA class to establish that the difference was not clinically important, as patients with Class IV heart failure did appear to respond better to dapagliflozin than those with Class III heart failure (see Table 5, below). While

acknowledging that the number of enrolled patients with NYHA Class IV heart failure was low, the sponsor argued that it was not biologically plausible that the treatment effect of dapagliflozin could be more pronounced in both the most severely and the least severely affected patients.

Furthermore, additional pre-specified analyses of the primary endpoint based on different measures of severity of heart failure (NT-proBNP, and/or left ventricular ejection fraction) did not identify a significant difference in treatment effect in patients with baseline measures at or below the median level compared to measures above the median. *Post hoc* analyses of treatment effect by continuous baseline left ventricular ejection fraction, by baseline NT-proBNP levels, and MAGGIC Risk Score[11,12] quintiles broadly supported a positive treatment effect of dapagliflozin, although the 95% CI for higher baseline NT-proBNP levels crossed unity, as did the 95% CI in the lowest and highest MAGGIC risk quintiles.

Table 5: DAPA-HF trial Primary endpoint and components by NYHA Class

	Dapa 10 mg (N = 2373)			Placebo (N = 2371)					
Subject characteristic Category	Number of subjects	Subjects with event n (%)	Event rate	Number of subjects	Subjects with event n (%)	Event rate	Hazard ratio	95% CI	Interaction p-value
Analysis of the primary composite endpoint by NYHA class									
NYHA class									0.0055
II	1606	190 (11.8)	8.2	1597	289 (18.1)	13.1	0.63	(0.52, 0.75)	
III	747	191 (25.6)	19.3	751	200 (26.6)	20.0	0.93	(0.76, 1.14)	
IV	20	5 (25.0)	19.8	23	13 (56.5)	51.0	0.41	(0.14, 1.21)	

Event rates are presented as the number of subjects with event per 100 patient years of follow-up

Hazard ratio for Dapa 10 mg vs placebo, confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model (score test) stratified by T2DM status at randomisation, with factors for history of HF hospitalisation, NYHA class, treatment group and the interaction between treatment group and NYHA class.

CI, confidence interval; Dapa, dapagliflozin; N, number of subjects in treatment group; n, subjects with an event; NYHA, New York Heart Association.

Dapagliflozin was statistically superior to placebo in the analyses of the secondary composite outcome of total (first and recurrent) heart failure hospitalisations and CV death. There were 567 and 742 events of CV death or hospitalisation for heart failure in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 16.3/ 100 PY and 21.6/100 PY of follow-up, respectively; the rate ratio was 0.75 (95% CI: 0.65, 0.88), p = 0.0002. Each of the two components of the composite endpoint contributed to the observed treatment effect.

Dapagliflozin was also statistically superior to placebo in improving patient reported outcomes according to the KCCQ-TSS questionnaire. Both the symptom frequency and symptom burden subdomains contributed to the overall treatment effect. The win ratio for the KCCQ-TSS was 1.18 (95% CI: 1.11, 1.26, p < 0.0001), in favour of dapagliflozin relative

[11] Meta-Analysis Global Group in Chronic (MAGGIC) Heart Failure Risk Score. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013; 34:1404–1413.
[12] The MAGGIC Risk Score calculator in heart disease presents 1 and 3 year all-cause mortality estimates for people with heart failure based on patient data, cardiac and comorbidity data.

to placebo. The mean (SD) change from Baseline at eight months in the KCCQ-TSS was 6.11 (18.65) in the dapagliflozin group and 3.30 (19.24) in the placebo group. A clinically relevant improvement or deterioration in KCCQ-TSS was defined as a change from Baseline of ≥ 5 points. The proportion of patients with an improvement in KCCQ-TSS of ≥ 5 points was higher in the dapagliflozin treatment group (57.4%) compared to the placebo group (50.0%). The proportion of patients with a deterioration in KCCQ-TSS of ≥ 5 points was lower in the dapagliflozin group (25.1%) compared to the placebo group (33.1%).

There was no statistically significant difference between the two treatment groups with regard to the composite endpoint of worsening renal function (dapagliflozin n = 28 (1.2%), placebo n = 39 (1.6%), HR: 0.71 (0.44, 1.16)). All-cause mortality was 11.6% (n = 276) in the dapagliflozin group and 13.9% (n = 329) in the placebo group. Time to death from any cause was not statistically analysed, based on hierarchical stopping rules.

Safety

The safety and tolerability of dapagliflozin in heart failure with reduced ejection fraction was evaluated based on assessments of serious adverse events (SAE), discontinuation of the study drug due to adverse events (DAE), adverse events (AE) of special interest, which included AEs suggestive of volume depletion, renal AEs, diabetic ketoacidosis (DKA), major hypoglycaemic events, fractures, AEs leading to amputation, and AEs leading to risk of lower limb amputation ('preceding events'), and changes in centrally-analysed clinical chemistry and haematology parameters. Non-serious AEs were collected for DAEs, AEs of special interest, AEs leading to potential endpoint events, AEs leading to interruption of study drug, and AEs leading to dose reduction of study drug.

Adverse events in the safety analysis set are summarised in Table 6 (shown below). The safety analysis set included 2368 participants in each arm who received at least one dose of randomised treatment. Five patients in the dapagliflozin arm and three patients in placebo arm were excluded from the safety analysis set as they did not receive any study treatment. The median duration of exposure was 17.8 months (range 0 to 28 months) in the dapagliflozin group and 17.6 months (range 0 to 28.3 months) in the placebo group. Over 90% of participants in each arm had been exposed for ≥ six months, over 80% in each arm had been exposed for ≥ 12 months, and around 10% had been exposed for ≥ 24 months. Less than 2% of participants in each arm required dose reduction at any time; the most common adverse event triggering dose reduction was hypotension, affecting 20 (0.8%) participants in the dapagliflozin group and 11 (0.5%) in the placebo group.

Table 6: DAPA-HF trial Summary of adverse events (safety analysis set)

	Number (%) of subjects[a]			
	On-treatment		On and off treatment	
AE category	Dapa 10 mg (N=2368)	Placebo (N=2368)	Dapa 10 mg (N=2368)	Placebo (N=2368)
Any AE with outcome = death	227 (9.6)	250 (10.6)	286 (12.1)	333 (14.1)
Any SAE (including events with outcome = death)	846 (35.7)	951 (40.2)	895 (37.8)	994 (42.0)
Any AE leading to discontinuation of IP	111 (4.7)	116 (4.9)	111 (4.7)	116 (4.9)
Any AE leading to dose interruption	284 (12.0)	349 (14.7)	284 (12.0)	349 (14.7)
Any AE leading to dose reduction	43 (1.8)	25 (1.1)	43 (1.8)	25 (1.1)
Any definite or probable diabetic ketoacidosis[b]	3 (0.1)	0	3 (0.1)	0
Any major hypoglycemic event[c]	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)
Any event of symptoms of volume depletion[d]	170 (7.2)	153 (6.5)	178 (7.5)	162 (6.8)
Any fracture[d]	48 (2.0)	47 (2.0)	49 (2.1)	50 (2.1)
Any renal AE[d]	141 (6.0)	158 (6.7)	153 (6.5)	170 (7.2)
Any amputation[e]	11 (0.5)	11 (0.5)	13 (0.5)	12 (0.5)

Source: Summary of Clinical Safety, Table 1.

(a) Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.(b) Events adjudicated as definite or probable diabetic ketoacidosis. (c) AE with the following criteria confirmed by the investigator: i) Symptoms of severe impairment in consciousness or behaviour; (ii) need of external assistance; (iii) intervention to treat hypoglycaemia; (iv) prompt recovery of acute symptoms following the intervention. (d) Based on pre-defined list of preferred terms. (e) Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma.

The on-treatment columns include AEs with an onset date on or after date of first dose and up to and including 30 days following last dose of study drug. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. DAE AE leading to discontinuation of IP. IP Investigational product. N Number of subjects in treatment group. SAE Serious AE. SAS Safety analysis set. Percentages are based on the total numbers of subjects in the treatment group (N).

In the *on-treatment period*, 227 patients (9.6%) in the dapagliflozin group and 250 patients (10.6%) in the placebo group who died due to AEs with an outcome of death. AEs resulting in death affecting ≥ 0.5% of patients in either treatment group (dapagliflozin versus placebo respectively), by System Organ Class (SOC) and Preferred Term (PT) were: SOC Cardiac Disorders (total 102 (4.3%) versus 120 (5.1%)): PT Cardiac Failure (42 (1.8%) versus 57 (2.4%)); and SOC General Disorders and Administration Site Conditions (total 68 (2.9%) versus 75 (3.2%)): PT Death (33 (1.4%) versus 38 (1.6%)); PT Sudden Cardiac Death (17 (0.7%) versus 27 (1.1%)); and PT Sudden Death (17 (0.7%) versus 7 (0.3%)).[13] AEs resulting in death by PT did not reach 0.5% in any other SOC.

Serious AEs were less frequent in the dapagliflozin group (846, 35.7%) than in the placebo group (951, 40.2%). The most frequent SAEs (dapagliflozin versus placebo) were cardiac failure (10.1% versus 13.7%) followed by pneumonia (3.0% versus 3.1%) and a range of CV events. SAEs of acute kidney injury occurred in 0.8% and 1.7% of patients in dapagliflozin and placebo groups, respectively. Adverse events resulting in discontinuation (dapagliflozin versus placebo, respectively) included cardiac failure (0.7%

[13] Derived from the clinical study report, Table 14.3.3.2; subjects with multiple events are counted once for each SOC/PT according to MedDRA version 22.0

versus 0.6%), dizziness (0.2% versus 0.2%), hypotension (0.2% versus 0.2%), urinary tract infection (0.2% versus 0.1%), renal impairment (0.1% versus 0.2%) and congestive cardiac failure (< 0.1% versus 0.3%).

Events suggestive of volume depletion, renal AEs, DKA, major hypoglycaemic events, fractures, amputations and preceding events for lower limb amputation were all considered AEs of special interest; most of these may be considered related to the treatment of patients with T2DM. Overall, the frequency of AEs of special interest were similar in the dapagliflozin and placebo groups with regard to renal events (renal impairment, acute kidney injury, renal failure, pre-renal failure, anuria, azotaemia, toxic nephropathy), fractures and amputations. The frequency of events suggestive of volume depletion (including hypotension, hypovolaemia, dehydration, syncope, orthostatic hypotension, blood pressure decreased, circulatory collapse and hypovolaemic shock) during the on-treatment period were slightly higher in the dapagliflozin group (7.2%) than in the placebo group (6.5%); this difference was also seen in the combined on-and-off treatment period.

Preceding events for lower limb amputations in the on and off treatment period were numerically higher in the dapagliflozin group than in placebo (155/2368, 6.5% versus 120/2368, 5.1%, respectively). The frequencies of lower limb amputation preceding events related to diabetes complications, particularly cellulitis, were equal in the two treatment groups (1.9% each); whereas preceding events related to peripheral vascular disease (dapagliflozin, 1.6% versus placebo, 0.9%) and to volume depletion (dapagliflozin, 2.9% versus placebo, 2.2%) were more frequently reported in the dapagliflozin group. While preceding events were reported more frequently in the dapagliflozin group, similar numbers of participants in each group experienced one or more amputations affecting the lower limb (dapagliflozin 13, placebo 12) at any time during the on and off treatment period. Of these, thirteen participants in the dapagliflozin group and ten participants in the placebo group experienced a preceding event before the subsequent amputation.

No events of DKA were reported among participants with heart failure with reduced ejection fraction in the absence of T2DM at baseline in either dapagliflozin or placebo arms; three participants with T2DM in the dapagliflozin arm and no participants in the placebo arm experienced events that were independently adjudicated as definite DKA. There was no difference between dapagliflozin and placebo arms in reports of major hypoglycaemic events: all reports occurred in patients with T2DM at Baseline.

Mean haematocrit and haemoglobin levels increased early in treatment and plateaued after month four in the dapagliflozin treatment arm, but not in the placebo arm. This effect of dapagliflozin has been described previously and is a known class effect of SGLT2 inhibitors. To date, no apparent relationship has been identified between the increased haematocrit and haemoglobin with increased thromboembolic events.

Over the follow-up period, no clinically important differences were reported between dapagliflozin arm and placebo arm with regard to other laboratory parameters or vital signs. No new safety signals were identified in the DAPA-HF trial, with the safety profile being consistent with the known safety profile for dapagliflozin in the treatment of patients with T2DM, with or without heart failure.

Clinical evaluator's recommendation

The clinical evaluator supports the application for registration for the intended use.

Risk management plan

The most recently accepted EU-risk management plan (RMP) was Version 15 (dated 9 August 2017, data lock point (DLP) 9 August 2017) and Australian-specific Annex

(ASA) Version 9 (dated 15 August 2018). In support of the extended indication, the sponsor has submitted draft EU-RMP version 18 (dated 24 October 2019; DLP 30 September 2019) and ASA version 11 (dated 8 November 2019).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 7.[14]

Table 7: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Urinary Tract Infections	ü*	ü†	ü	–
	Diabetic Ketoacidosis, including events with atypical presentation	ü*	ü§‖	ü	–
	Renal impairment	ü*	ü†	ü	–
Important potential risks	Liver injury	ü*	ü†	–	–
	Amputation (ASA) / Lower limb amputation (EU-RMP)	ü*	ü‡	–	–
	Bladder cancer	ü*	ü†	–	–
	Breast cancer	ü*	ü†	–	–
	Prostate cancer	ü*	ü†	–	–
Missing information	Nil				

* targeted questionnaires; † observational study; ‡ meta-analysis; § nonclinical study; ‖ retrospective cohort study

Summary

The sponsor has removed Australia-specific safety concerns (urosepsis, malignancy, patient with body mass index > 45, off-label use) that had been required for the diabetes indications. This is acceptable. No new safety concern is proposed for the heart failure indication. The summary of safety concerns is acceptable.

Routine pharmacovigilance includes targeted questionnaires for all risks. Additional pharmacovigilance activities are ongoing to support the diabetes indications. No

[14] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

additional pharmacovigilance activity has been proposed in relation to the heart failure indication. The pharmacovigilance plan is acceptable.

The routine risk minimisation activities are acceptable.

Additional risk minimisation activities (prescriber education, patient brochures) have recently been discontinued for the diabetes indications, and do not need to be reintroduced for the heart failure indication.

There are no new or outstanding recommendations.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The Forxiga EU-Risk Management Plan (RMP) (version 18, dated 27 October 2019, data lock point 30 September 2019), with Australian Specific Annex (version 11.0, dated 8 November 2019), included with submission PM-2019-05370-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the periodic safety update report (PSUR) requirement:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.*

Delegate's comments on the risk management plan

No new safety concerns were identified in association with the extension of indications to include heart failure with reduced ejection fraction in patients who do not have T2DM. Routine pharmacovigilance includes targeted questionnaires for all risks. Additional pharmacovigilance activities to support the diabetes indications are ongoing. No additional pharmacovigilance activity has been proposed in relation to the heart failure indication.

The RMP evaluator recommends that dapagliflozin should be included in the Black Triangle Scheme,[15] on the basis that using dapagliflozin in patients with heart failure who

[15] Post the second round of RMP evaluation and following further consultation between the RMP evaluator and the sponsor, the sponsor has presented acceptable arguments for exclusion from the Black Triangle Scheme. The RMP evaluator updated their advice to the Delegate regarding inclusion on the Black Triangle Scheme and the sponsor's risk management strategy was considered to be approvable to the satisfaction of the TGA Delegate. Inclusion on the Black Triangle Scheme was not a requirement for approval.

do not have T2DM is an extension of indication to a significantly different disease or condition. The medicine will be used by a new prescriber speciality in a broader population, and the medicine will be discussed in new chapters of therapeutic guidelines.

The sponsor argues against inclusion in the Scheme on the basis that the safety profile is not significantly different between T2DM patients and patients without diabetes with heart failure with reduced ejection fraction. In a response to the second round evaluation reports, the sponsor also disagreed that the prescribers for patients with heart failure without diabetes would be substantially different from prescribers for patients with heart failure with diabetes. The sponsor further argued that all of the prescribers will already be familiar with SGLT2 inhibitors by reference to published treatment guidelines. Both referenced guidelines were specific to the management of hyperglycaemia in T2DM.

The sponsor has agreed to the following conditions of registration recommended by the RMP evaluator:

Regarding the risk management plan and Australian specific annex:

> *The Forxiga EU-Risk Management Plan (RMP) (version 18, dated 27 October 2019, data lock point 30 September 2019), with Australian Specific Annex (version 11.0, dated 8 November 2019), included with submission PM-2019-05370-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

Regarding submission of periodic safety update reports:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Risk-benefit analysis

Delegate's considerations

Proposed indication

The sponsor requested approval of the following extension of indication for dapagliflozin:

> *Forxiga is indicated in adults for the treatment of heart failure with reduced ejection fraction.*

In the dosage and administration instructions, the sponsor included additional information:

> The recommended dose of Forxiga is 10 mg taken orally once daily at any time of the day regardless of meals. Forxiga can be used in conjunction with other heart failure therapies.

The efficacy data provided by DAPA-HF trial supports the proposed indication, however the evidence applies only when dapagliflozin is used as an adjunct to established standard of care. The addition of 10 mg dapagliflozin once daily to an established treatment regime was statistically significantly superior to addition of placebo in reducing the incidence of the composite primary efficacy end point of CV death, hospitalisation for heart failure or urgent heart failure visit, decreasing the risk of experiencing the composite endpoint by

26% (95% CI: 15%, 35%). Treatment with dapagliflozin delayed the time to the first composite endpoint event relative to placebo, with the Kaplan-Meier curves separating in favour of dapagliflozin early in treatment and continuing to separate up to 24 months of follow-up. The secondary efficacy endpoints, including important patient reported outcomes, supported the primary outcome. However, the study did not establish, nor was it designed to establish, that dapagliflozin monotherapy has a place in the treatment of heart failure. The proposed instructions regarding dosage and administration do not appear to reflect this limitation. To accurately reflect the details of the supporting evidence, it would be appropriate to amend the proposed indication to:

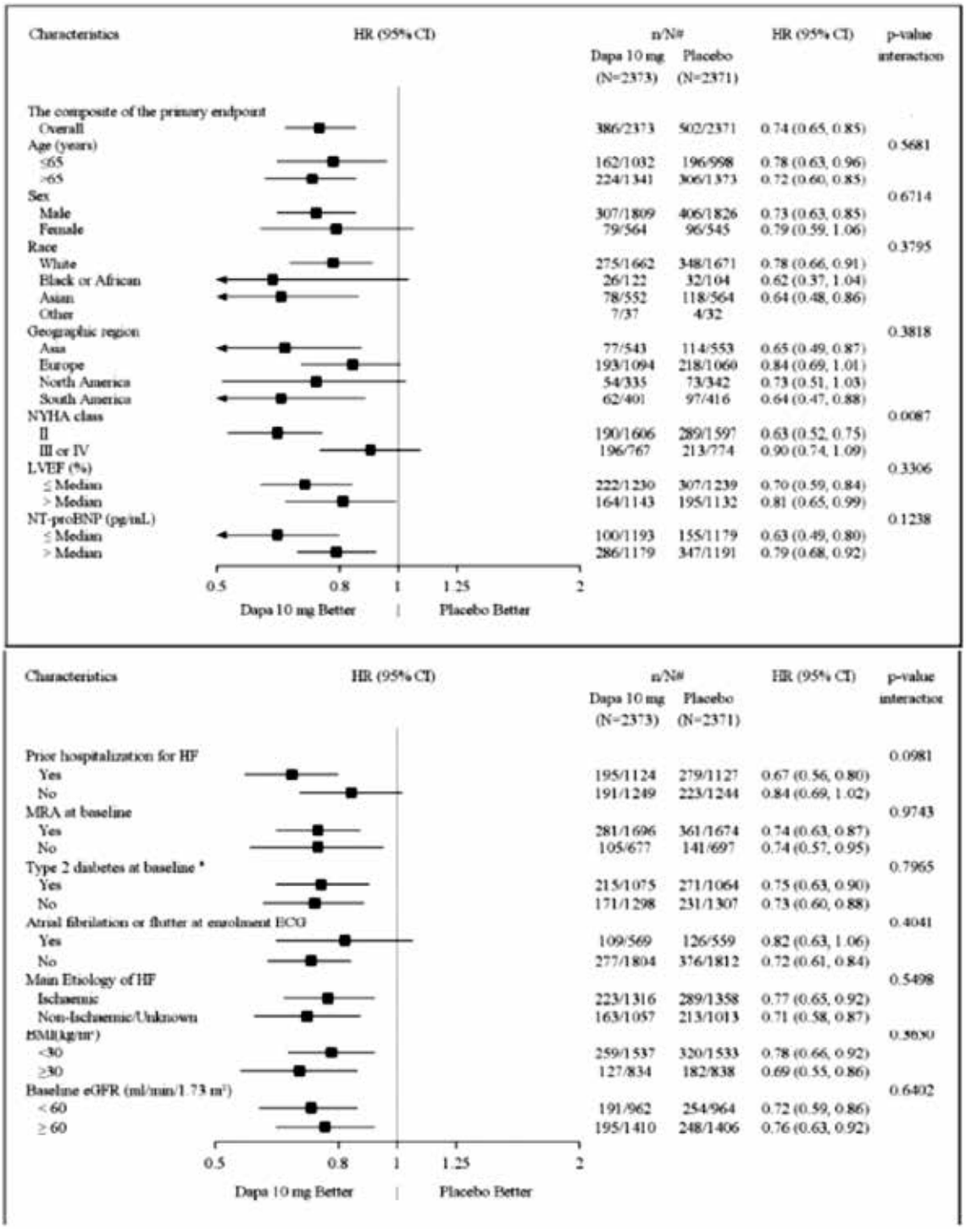
> *Forxiga is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fraction, as an adjunct to standard of care therapy.*

This wording reflects the study evidence and aligns with indications for other medicines used in combination therapy for heart failure. Additional changes to the dosage and administration and other sections of the PI are addressed elsewhere [inclusion of comments on the PI is beyond the scope of the AusPAR].

Deficiencies of the data

While the efficacy of dapagliflozin in the treatment of patients with NYHA Class II heart failure with reduced ejection fraction has been satisfactorily established, the evidence in the more severe Class III and IV patients is somewhat equivocal. Study participants with Class IV heart failure represented only around 1% of the study population and in the pre-defined statistical analysis by sub-groups the Class III and Class IV groups were combined. While the hazard ratio for the combined group and indeed for the separate groups indicated a possible benefit for dapagliflozin, the 95% CI crossed unity in each case. Particularly in the case of Class IV heart failure participants, while the HR of 0.41 indicates a potentially better response to dapagliflozin than in Class II heart failure (HR 0.63), and the absolute number of primary events is lower in the dapagliflozin group than in the placebo group (5/20 compared to 13/23), it is reasonable to accept that the lower heart failure is a chance finding. The additional analyses included in attachment 2 support a positive effect for dapagliflozin in general, however, depending on the nature of the analysis, confidence intervals for the HR remain close to, or cross, unity. This uncertainty regarding efficacy in Class III and IV heart failure is unlikely to be resolved without further investigation. The treatment effect did not reach nominal statistical significance (upper confidence limit above 1) in women, in patients of Black or African origin, in enrolled patients from North America, in patients who had not had a prior hospitalisation for heart failure and in patients with atrial fibrillation or flutter at the time of the enrolment electrocardiogram (see Figure 1, below). In most cases this would appear to be a result of lower enrolments from these populations; only those patients who had not had a prior heart failure hospitalisation were represented in higher numbers than in the comparative sub-groups. Completing two years of follow-up in the entire population may assist in clarifying whether the numerical difference in CV deaths and heart failure events in the NYHA Class III and Class IV heart failure, and in the other population subgroups, is clinically meaningful. The indication recently approved by the FDA includes all three NYHA Classes II to IV. The Health Canada product monograph is silent in regard to relative efficacy in the different NYHA classes, apart from reporting that the DAPA-HF clinical trial enrolled patients with Class II to IV heart failure. The Canadian product monograph included Forest plots depicting treatment effect by sub-groups with data for Class II versus Class III or IV, left ventricular ejection fraction ≤ median versus > median and NT-proBNP ≤ median versus > median, and other population sub-groups. The same information will also be included in the Australian PI.

Figure 1: DAPA-HF trial Forest plot of results for the primary outcome (full analysis set)



The median follow-up time in the DAPA-HF trial was around 18 months. At the data lock point, only around 10% of the study population had been exposed to treatment for two years or more. While the event-driven efficacy endpoint was achieved, the period of exposure is likely to have been too short to unveil any rare or unusual long term safety issues. This is partly mitigated by post-marketing safety reports on long-term use of dapagliflozin in patients with diabetes. In general, the safety profile of dapagliflozin in patients with heart failure with reduced ejection fraction followed for up to 24 months was similar to the established safety profile in longer term use in diabetes. Indeed, some of the safety issues associated with dapagliflozin use for the treatment of diabetes were not

reported at a higher rate in patients with heart failure with reduced ejection fraction treated with dapagliflozin than with placebo, irrespective of concomitant diabetes.

Conditions of registration

The sponsor has agreed to the following conditions of registration:

> *The FORXIGA EU-Risk Management Plan (RMP) (version 18, dated 27 October 2019, data lock point 30 September 2019), with Australian Specific Annex (version 11.0, dated 8 November 2019), included with submission PM-2019-05370-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*
>
> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes.*
>
> *Note that submission of a PSUR does not constitute an application to vary the registration.*

The RMP evaluator recommended that dapagliflozin should be included in the Black Triangle Scheme, which was implemented in 2018 to gather additional adverse event reports for new prescription medicines and medicines being used in a different population or a different disease or condition.[16] Inclusion in the Black Triangle Scheme does not imply that there is a safety issue with the medicine. In view of the relatively short safety follow-up period presented in the DAPA-HF trial study report, the Delegate supports this recommendation. Additionally, the pre-clinical evaluation indicates that the mechanism of action of dapagliflozin in heart failure may not solely be related to increased urinary excretion of glucose as has been shown in the treatment of hyperglycaemia in patients with diabetes. While acknowledging the sponsor's assertion that the specialists who treat patients with heart failure with reduced ejection fraction are likely to be familiar with dapagliflozin as they would have treated patients with diabetes as well as those without diabetes, the long term safety data for patients in the absence of concomitant diabetes is lacking. This and the other proposed conditions of registration align with TGA guidelines and usual practice.

The Delegate supports the recommended condition of registration regarding the Black Triangle Scheme:

> *Forxiga (dapagliflozin) is to be included in the Black Triangle Scheme. The PI and CMI for Forxiga must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.* [16]

[16] Post the second round of RMP evaluation and following further consultation between the RMP evaluator and the sponsor, the sponsor has presented acceptable arguments for exclusion from the Black Triangle Scheme. The RMP evaluator updated their advice to the Delegate regarding inclusion on the Black Triangle Scheme and the sponsor's risk management strategy was considered to be approvable to the satisfaction of the TGA Delegate. Inclusion on the Black Triangle Scheme was not a requirement for approval.

Proposed regulatory action

Pending advice from Advisory Committee on Medicines (ACM) and the sponsor's Pre-ACM Response, the Delegate considers the benefit/risk profile to be positive and recommends approval for the indication:

> *Forxiga is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fraction, as an adjunct to standard of care therapy.*

Outstanding issues

The final version of the product information and consumer medicine information will be negotiated with the sponsor.

Conclusion

The sponsor had no reason to say, at the time, that the application for dapagliflozin should not be approved for registration.

Advisory Committee considerations[17]

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.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. What is the opinion of the committee on restricting the indication to symptomatic heart failure with reduced ejection fraction and use only in conjunction with other heart failure therapies?

The committee was of the view that the indication should be restricted to use in patients with symptomatic heart failure with reduced ejection fraction (with or without type 2 diabetes mellitus) in conjunction with other heart failure therapies to ensure that use is targeted toward those who will gain the most benefit.

2. What is the opinion of the committee regarding the long term safety of dapagliflozin in adults with symptomatic heart failure in the absence of T2DM, given that the median follow-up period in the DAPA-HF trial was 18 months?

The ACM noted that dapagliflozin has been utilised in the type 2 diabetes population for several years.

The ACM agreed that owing to the longer history of use of dapagliflozin in patients with type 2 diabetes, and in the absence of new or different safety concerns arising from the DAPA-HF trial, the relatively short term safety follow-up in this study is not an issue. Patients with heart failure commencing on dapagliflozin will be monitored by a subspecialist group.

[17] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

3. The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

With regard to the phrasing of the PI, the ACM advised that the particular classes of drugs that are used in conjunction with dapagliflozin do not need to be individually specified within the PI as this is a clinical decision to be made by the treating physician based on the patient's individual circumstances.

The Delegate also requested advice regarding the proposed removal of cautionary text in the PI concerning volume depletion. The committee was of the view that the cautionary text should be retained in the PI as it provides a warning to patients and prescribers about a real issue that can have serious implications for a small number of patients. The ACM noted that volume depletion appears to be a class effect, and that cautionary text concerning volume depletion is also included in the PI of other SGLT2 inhibitors.

Conclusion

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

> *Forxiga is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fraction, as an adjunct to standard of care therapy.*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Forxiga (dapagliflozin, as propanediol monohydrate) 10 mg film-coated tablets indicated for the following extension of indications:

> ***Heart failure***
>
> *Forxiga is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fraction, as an adjunct to standard of care therapy (see section 5.1 Pharmacodynamic properties).*

The full indications are now:

> ***Type 2 diabetes mellitus***
>
> *Glycaemic control*
>
> *Forxiga is indicated in adults with type 2 diabetes mellitus:*
>
> - *as monotherapy as an adjunct to diet and exercise in patients for whom metformin is otherwise indicated but was not tolerated.*
> - *as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control when diet and exercise have failed to provide adequate glycaemic control and there are poor prospects for response to metformin monotherapy (for example, high initial haemoglobin A1c [HbA1c] levels).*
> - *in combination with other anti-hyperglycaemic agents to improve glycaemic control, when these together with diet and exercise, do not provide adequate glycaemic control (see section 5.1 Pharmacodynamic properties – Clinical trials and section 4.4 Special warnings and precautions for use for available data on different add-on combination therapies.*
>
> *Prevention of hospitalisation for heart failure*

Forxiga is indicated in adults with type 2 diabetes mellitus and established cardiovascular disease or risk factors for cardiovascular disease to reduce the risk of hospitalization for heart failure (see section 5.1 Pharmacodynamic properties – Clinical trials).

Heart failure

Forxiga is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fraction, as an adjunct to standard of care therapy (see section 5.1 Pharmacodynamic properties).

Specific conditions of registration applying to these goods

- The Forxiga EU-Risk Management Plan (RMP) (version 18, dated 27 October 2019, data lock point 30 September 2019), with Australian specific annex (version 11.0, dated 8 November 2019), included with submission PM-2019-05370-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Forxiga approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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