TAR 382 – SGLT-2 inhibitors for type two diabetes mellitus (T2DM) with established high cardiovascular disease (CVD)

This assessment provides an estimate of likely cost effectiveness range of SGLT 2 inhibitors with established high cardiovascular disease risk

A summary of the proposal is provided in the table below.

PROPOSAL OVERVIEW
Pharmaceutical SGLT-2 inhibitor – Modelled as empagliflozin Once daily tablet 10mg or 25mg, packs of 30 tabs
Supplier Boehringer Ingelheim
Proposed Indication Type two diabetes mellitus (T2DM) with high cardiovascular disease risk
Dosing Once daily tab of 10mg or 25mg
Pharmaceutical Price List price $58 56 per pack of 30 Price after rebate Withhel per pack of 30 Price per daily dose Withhe (Supplier offer current as of July 2019).
PTAC PRIORITY Cardiovascular outcome evidence of SGLT-2 inhibitor class reviewed by PTAC February 2019 and the Diabetes Subcommittee in March 2019 No formal recommendation given
PHARSIGHT REFERENCE Link Model: \\pharmhouse\FD\CUAs\SGLT2 GLP1 for type 2 diabetes

Executive Summary

This Technology Assessment Report (TAR) evaluates the cost effectiveness of a class of agents called sodium glucose transport protein two (SGLT 2) inhibitors as an add on therapy for people with type two diabetes with high CVD risk. Type two diabetes is a chronic disease categorised by high blood sugar levels (hyperglycaemia) that occur as a result of insufficient production of insulin, the hormone that regulates blood sugar levels, or an ineffective response to the insulin the body produces. The disease is associated with severe long term consequences including microvascular consequences such as neuropathy, retinopathy and nephropathy, and macrovascular consequences including cardiovascular disease, stroke and heart failure.

Review of Cost Utility Analyses

The cost effectiveness analyses provided by the supplier with their application to PHARMAC was conducted prior to the publication of the long term cardiovascular outcomes data. Consequently, the CUA was based on simulated changes in the rate of macrovascular and microvascular complications from changes in surrogate endpoints such as a change in blood pressure, HbA1c and weight. PHARMAC staff have therefore undertaken a new CUA which considers newer published evidence of improved cardiovascular and renal outcomes

PHARMAC staff reviewed several technology assessments reports for SGLT 2 inhibitors published by NICE (United Kingdom) and PBAC (Australia) As above, consideration of these pharmaceuticals occurred prior to the publication of long-term cardiovascular and renal outcome data These reports generally recommended funding the agents on a cost minimisation basis to existing anti-diabetic agents citing non-inferiority.

Summary of PHARMAC Cost-Utility Analysis

A cost utility analysis (CUA) was undertaken by PHARMAC staff to estimate the cost effectiveness of SLGT-2 inhibitors for type two diabetes compared to current best practice for diabetes and cardiovascular disease. The clinical effectiveness component of the economic analysis was based on the SGLT-2 empagliflozin with the pivotal evidence coming from the EMPAG-Reg outcome trial. The model only considered outcomes where the difference between the intervention (empagliflozin) and comparator (placebo/best standard of care) was statistically significant. The outcomes included were all-cause death, heart failure hospitalisation, progression to microalbuminuria and initiation of renal replacement therapy. In addition, the model considered a reduction in insulin units for those on insulin and a SGLT 2 inhibitor and a delay in the progression to insulin therapy for those taking a SGLT 2 inhibitor but not on insulin at baseline The model considered the costs and QALYS gained over a 10 year time horizon.

The incremental cost is estimated to be Withheld with a QALY gain of 0.27. The estimated QALYs per $1million is Withheld under (cost per QALY of Withheld) The likely cost-effectiveness range (Withheld) incorporates likely variations in the probabilities of death, heart failure hospitalisation and progression to macroalbuminuria as well as variation in the utility values used, the cost of macroalbuminuria and heart failure hospitalisation The possible cost effectiveness range (Withheld) incorporates the possibility of no benefit from insulin (usage and delay to progression), up to 35 months delay in progression to insulin and a potential commercial offer.

Summary of Budget Impact Analysis

Data from the PREDICT cohort in Auckland was applied to the New Zealand diabetes population to determine that Withheld people in New Zealand have type two diabetes and a cardiovascular risk profile of greater than 15% and would, therefore, be eligible of treatment with an SGLT 2 inhibitor

The net cost to the community/hospital pharmaceutical schedule is expected to be Withheld Withheld in year 1 with a 5 year net present value (NPV) of Withheld under The ~~net~~ cost to DHBs is expected to be $0.28 million in year 1 with a 5-year NPV of $3.63 million.

1. Proposal Overview

1.1 Summary

- PHARMAC has received applications for 10 new diabetic agents (see table below).

SGLT 2 inhibitors	DPP4 inhibitors	GLP1 agonists
Canagliflozin	Linagliptin	Exenatide
Dapagliflozin	Saxagliptin	Liraglutide
Empagliflozin	Sitagliptin	Lixisenatide
Ertugliflozin*	Vildagliptin	Albiglutide*
	Alogliptin*	Dulaglutide*
		Semaglutide*
* No application to PHARMAC has been received for these agents as of Jan 2019. Note: Proposals full history can be viewed by opening the linked hyperlinks		

- PTAC and the Diabetes Subcommittee reviewed several of these agents in the early 2010s (see hyperlinks to PHARMAC Application Tracker in above table) concluding that the evidence of clinical efficacy was of moderate quality and strength and that, in general, a reduction in HbA1c of approximately 0.5% to 1% could be expected. The committees noted concern with the lack of long term data on efficacy as a result of changes in surrogate endpoints and the lack of evidence supporting clinically significant benefits other than change in HbA1c.

- In 2016, new evidence was reviewed by the Diabetes subcommittee regarding longer term cardiovascular and renal clinical benefits of treatment with these new agents The Committee considered it would be appropriate going forward to consider the clinical efficacy of each class separately.

- In 2017 and 2018, PTAC has reviewed the long term cardiovascular disease outcome data for the following agents: Empagliflozin, Exenatide, Liraglutide and Dapagliflozin Exenatide was reviewed and received a low priority recommendation. Empagliflozin and Liraglutide received a High priority recommendation while Dapagliflozin received a medium priority recommendation for type 2 diabetics with established high CVD disease risk.

- At **PTAC in February 2019**, the committee considered the available cardiovascular outcome data for the three classes of new diabetes agents. Some key minutes from the meeting are noted below:

    - "The Committee considered that based on currently available data overall the various DPP4 agents appeared to have the same or similar effect and are safe within the glucose-lowering algorithm but have neither positive or negative cardiovascular effects "
    - "The Committee considered that GLP1 trials show cardioprotective effect with respect to mortality, with positive effects for all agents in this class observed throughout the study duration which was indicative of a class effect from these agents The Committee considered that evidence indicates GLP1 could provide benefit for a wider patient population than just those with established CVD."

- “The Committee considered that based on published literature to date SGLT2i appear to have some benefits in reduction of hospital admission for heart failure and slowing progression of composite renal outcomes, with some showing a reduction in cardiovascular mortality, however the evidence of cardiovascular benefit is in patients with established heart disease only. The Committee considered that SGLT2i likely provided the greatest benefit of the three antidiabetic agent classes for patients with or at high risk of heart failure.”
- “The Committee considered that currently published longer term follow up data for newer antidiabetic agents do not yet show definitively the renal benefit for patients with renal 37 disease, however SGLT2i likely provide benefit for patients with progressive decline in eGFR ”
- “The Committee considered that while the literature appeared to be unresolved as to similarity of outcomes from the various newer antidiabetic agents, members considered it was likely each of these classes of agents had the same or similar within class therapeutic effects as indicated by real world studies”

- At the **Diabetes Subcommittee meeting in March 2019**, the committee considered the available cardiovascular outcome data for the three classes of new diabetes agents Some key minutes from the meeting are noted below:

  - “The Subcommittee considered that based on the currently available literature the DPP-4 inhibitors as a class have similar glucose lowering therapeutic effects but the effect of the class on cardiovascular outcomes is neither inferior or superior to current treatment.”
  - “The Subcommittee considered that cardiovascular outcome data for GLP 1 receptor agonists available to date shows a consistent signal for a reduction in all cause mortality, cardiovascular mortality, and heart failure hospitalisation can be achieved with each GLP-1 receptor agonist agent within the class. The Subcommittee considered that this positive therapeutic effect from GLP-1 receptor agonists appears to occur irrespective of baseline cardiovascular or renal risk. The Subcommittee considered that in terms of cardiovascular outcomes GLP 1 agents provided the same or similar level of benefit for people with T2DM.”
  - “The Subcommittee considered that current evidence for SGLT2 inhibitors suggests that there is likely a positive therapeutic benefit on the risk of heart failure hospitalisation and progression of renal composite outcomes with SGLT2 inhibitor agents, with some SGLT2 inhibitors also demonstrating a positive effect on the risk of major adverse cardiovascular events (MACE), cardiovascular mortality and all cause mortality The Committee considers that for an established cardiovascular risk T2DM population the evidence clearly demonstrates a class effect in terms of cardiovascular outcomes and there is also a trend, although not as significant, that this is also the case for a high cardiovascular risk population without established disease.”
  - “The Subcommittee acknowledged there is currently a level of uncertainty due to the variation of cardiovascular disease and renal characteristics of participants in the trial populations but overall considered there is a similar therapeutic benefit in terms of cardiovascular outcomes within the SGLT2 inhibitor class The Subcommittee noted that internationally this uncertainty is recognised in guidelines, however considered that as more evidence becomes available it is likely class effects will be clearly seen.”
  - “The Subcommittee considered that current evidence supports class effects with the classes of antidiabetic agents in terms of renal benefits for T2DM patients ”

This TAR is reflective of the SGLT-2 inhibitor class of new anti-diabetic agent.

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

Table 1: - PICO

PICO	
POPULATION	Type two diabetes patients with high cardiovascular disease risk. Special authority below (Source. Diabetes Subcommittee March 2019) **Initial application from any medical practitioner.** Approvals valid without renewal for applications meeting the following criteria: All of the following: 1. Patient has type 2 diabetes; and 2 Patient has not achieved target HbA1c (of less than 64mmol/mol) despite maximum tolerated doses of oral antidiabetic agents and/or insulin for at least 6 months; and 3 Patient has 5 year absolute cardiovascular disease risk of 15% or greater according to a validated diabetes cardiovascular risk assessment calculator; and 4 Treatment is used to be used in conjunction with other measures to reduce cardiovascular risk in line with current standard of care; and 5. Treatment must be used as adjunct to oral antidiabetic therapy and/or insulin.
INTERVENTION	SGLT 2 inhibitor (Empagliflozin selected as the agent to represent the class)
COMPARISON	Placebo (intervention is an add-on therapy to best standard of care)
OUTCOME	• Decrease in all-cause mortality • Decrease heart failure hospitalisation • Improved renal outcomes (Delay in progression to macroalbuminuria and renal replacement therapy) • Delayed progression to insulin

1.2 Patient Population

Type two diabetes (T2DM) is a chronic disease categorised by high blood sugar levels High blood sugar levels or hyperglycaemia occur due to insufficient production of insulin, the hormone that regulates blood sugar levels, or an ineffective response to the insulin the body produces.

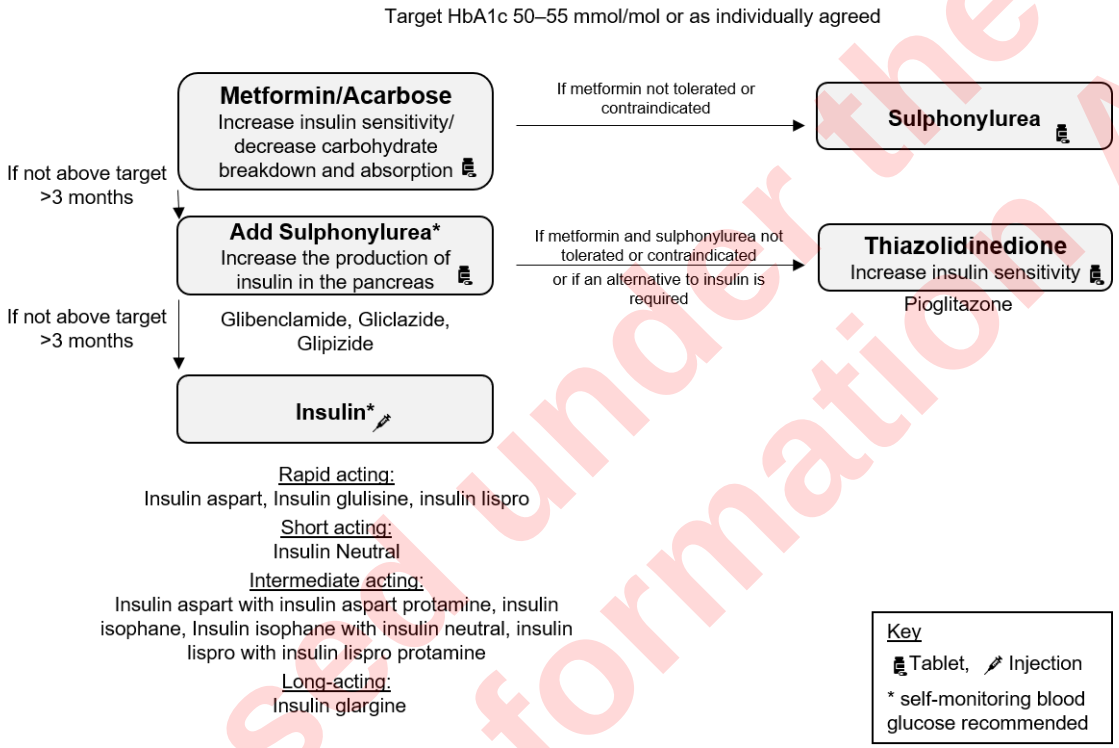
Diabetes is a highly prevalent condition with 245,700 people recorded in the Ministry of Health Virtual Diabetes Register of New Zealand in 2017. T2DM patients represent approximately 90% of these registrations.

Diabetes has several serious long term consequences. These include microvascular complications including peripheral neuropathy, diabetic retinopathy and diabetic nephropathy, and macrovascular complications which include ischaemic heart disease, stroke and peripheral vascular disease The risk of developing diabetes complications is reduced with good blood pressure, blood glucose and blood cholesterol control but increases with diabetes duration The occurrence and rate of progression of diabetes complications are notably higher for high risk populations (Māori, Pacific and South Asian populations). Cardiovascular disease is one of the largest disease burdens associated with T2DM in respect to both morbidity and mortality.

1.3 Current Treatment in New Zealand

The current diabetes treatment paradigm for T2DM and the funded pharmaceuticals in New Zealand are outlined in Figure 1 below PHARMAC staff note that as of October 2018, vildagliptin (a DPP-4 inhibitor) and vildagliptin/metformin combination have been funded without restriction and so are also available for the treatment of New Zealand patients with T2DM (Note: this is not included in the figure below).

Figure 1: New Zealand diabetes treatment paradigm (not updated to include vildagliptin)



Source: Diabetes Subcommittee Paper, Antidiabetic agents March 2019 (A1242797)
Note: Vildagliptin was funded after this graphic was produced. Vildagliptin would provide another line of therapy before insulin or could be added to the treatment regimen of those already on insulin.

1.4 Intervention

Sodium glucose cotransporter 2 inhibitors (SGLT 2 inhibitors) are a once daily oral formulation that functions by limiting glucose absorption in the kidneys, increasing the amount of glucose that is expelled in the urine and reducing the amount of glucose present in the blood. Use of SGLT-2 inhibitors therefore require an adequate degree of kidney function The likelihood of genital and urinary tract infections is increased with the use of SGLT-2 inhibitors

Empagliflozin was chosen as the representative agent within the SGLT 2 inhibitor class Empagliflozin is a once daily tablet at a dose of either 10mg or 25mg. Treatment is an add-on therapy to existing diabetes medication, and it expected to be continued unless unacceptable toxicity occurs

2. Health Benefits

2.1 Clinical Evidence

Table 2 below summaries the key pivotal trial for the SGLT 2 inhibitor, Empagliflozin.

Table 2: Summary of EMPA REG Outcome trial for Empagliflozin

Trial (Citation)	EMPAG-Reg outcome trial Cardiovascular impact (Zinman et al , N Engl J Med 2015;373:2117 28) Renal benefit (Wanner et al, N Engl J Med 2016; 375:323-33)
Study design	Randomised double-blinded, placebo controlled trial
Strength and quality of evidence	PTAC in November 2017 did not comment on the strength and quality of the EMPAG REG trial specifically
Population	7,028 people with T2DM and established cardiovascular disease (previous MI, coronary artery disease, unstable angina, previous stroke, peripheral artery disease)
Intervention(s)	Once daily tablet 10mg or 25mg (n=4,687)
Comparator(s)	Once daily placebo (n=2,333)
Duration	Median duration of treatment 2.6 years Median observation time 3.1 years
Results - clinical effectiveness	• Major Adverse Event (MACE) Hazard ratio (HR) 0 86 (95 02% Confidence interval (95.02%CI) 0.74-0.99 • Death from cardiovascular disease: HR 0.62 95%CI 0.49-0.77 • Death from any cause: HR 0.68 95%CI 0 57 0 82 • Hospitalisation from heart failure: 0 65 95%CI 0 50-0 85 • Fatal or non-fatal myocardial infarction: HR 0 87 (0 70-1 09) • Fatal or non-fatal stroke: HR 1.18 95%CI 0.89-1.56 • Hospitalisation for unstable angina: HR0.99 (0.74-1.34)
Results - safety	• Any adverse event: 91 7% placebo, 90 2% Empagliflozin • Adverse event leading to discontinuation: 19 4% placebo, 17 3% Empagliflozin • Adverse events that had a statistically significant difference between intervention and comparator: Female urinary tract infection(UTI) (40.6% placebo, 35.4% Empagliflozin), genital infection (1.8% placebo, 6.4% Empagliflozin), acute renal failure (6 6% placebo, 5 2% Empagliflozin), acute kidney injury (1 6% placebo, 5 2% Empagliflozin)
Interpretation of evidence	PTAC November 2017 "The Committee noted that the EMPA REG OUTCOME was designed as a safety trial, not an efficacy trial. The Committee noted that it reported improvements over placebo in death from any cause, death from cardiovascular causes, hospitalisation for heart failure, and the study's composite endpoint However, members considered it did not demonstrate improvements in all other measured outcomes, such as rates of myocardial infarction, cerebrovascular accident, transient ischaemic attacks, revascularisation, or admission for unstable angina."

Cardiovascular outcome evidence of SGLT 2 inhibitor class was also reviewed by PTAC February 2019 and the Diabetes Subcommittee in March 2019

3. Supplier and International Cost-Utility Analyses

3.1 Cost-Utility Analysis in Application

Empagliflozin

An economic analysis of empagliflozin was included in the application from the supplier received in August 2017. The analysis was a time to event analysis from the health system perspective with a life time horizon and a 3 5% annual discount rate The baseline characteristics of the modelled cohort (average age 63) and the time to event was informed by the EMPA REG study cohort. The model functions by calculating the time to event based on several patient characteristics and whatever event is predicted to occur earliest is the event to occur. If the event is not fatal, the calculation reoccurs until a fatal event occurs or the model time horizon is reached. The model included time to event data for the following 10 events: non fatal MI, non fatal stroke, hospitalisation for unstable angina, hospitalisation for HF, TIA, coronary revascularisation procedure, CV death, development of macroalbuminuria, renal injury (defined as a doubling of serum creatinine, with eGFR <45 ml/min), and renal failure (defined as need for renal replacement therapy)

The model considers pharmaceutical costs, pharmacy dispensing fees and health care costs associated with managing acute events (DRG related costs) Long-term disease management costs with the exception of renal failure (haemodialysis only) were not included to reduce the risk of double counting costs that are incurred in the model with the occurrence of subsequent events. The utility value for T2DM was 0.719. Utility decrements were then applied to this on the occurrence of events (myocardial infarction, stroke, heart failure, transient ischemic attack, revascularisation, macroalbuminuria, renal injury, renal failure) ranging between 0 03 to 0 07 and with recurrent events (-0.01 to -0.08). The mean duration of survival and hence treatment in the model was reported to be 14.3 year for empagliflozin and 12 years for placebo.

The base case analysis had an incremental cost of Withheld and an incremental QALY gain of 1.24 resulting in an ICER of Withheld or With QALYs per million dollars spent. The analysis was most sensitive to the discount rate.

PHARMAC staff have reviewed the CUA and note the following:

- The information to calculate time to event from the trial and in a New Zealand population is not available to PHARMAC.
- The analysis includes events which were found to not be statistically significantly different between empagliflozin and comparator, and a clinically meaningful difference was not evidenced

PHARMAC have therefore undertaken a CUA which only considers statistically significant differences in therapy and considers the probability of events rather than time to event analysis for which data was not available.

3.2 International Cost-Utility Analyses

Australia (PBAC)

Canagliflozin and dapagliflozin were recommended for funding by PBAC at their meeting in July 2013 on the basis of cost minimisation with sitagliptin. Since then both canagliflozin and dapagliflozin have been re-reviewed by PBAC on several occasions to have the eligibility criteria widened or reconsidered. Empagliflozin was recommended to be funded in November 2015 based on being cost neutral to dapagliflozin At the time of writing this TAR (September 2019), dapagliflozin and empagliflozin were available in combination with metformin and a sulfonylurea, in combination with insulin or in combination with metformin and a gliptin The fixed dose combination of dapagliflozin or empagliflozin with metformin was also available, as was an empagliflozin with linagliptin fixed dose combination. Canagliflozin was delisted in August 2015 as it was "longer being commercially viable at the reduced price" (Source)

United Kingdom (NICE)

Dapagliflozin (TA288 June 2013), Canagliflozin (TA315 June 2014) and Empagliflozin (TA336 March 2015) were reviewed and recommend for funding in dual therapy, triple therapy or in combination with insulin in 2013, 2014 and 2015 respectively All three technology assessments (TA) were conducted before the long-term cardiovascular outcome data was published The previous assessments of cost-effectiveness were therefore based simulating changes in the occurrence of diabetes complications as a result of changes in surrogate markers HbA1c, blood pressure and BMI rather than the cardiovascular outcome data that is now available.

In May 2016, NICE published TA390 which looked at all three SGLT 2 inhibitor agents for monotherapy use if metformin is contraindicated or not tolerated. The guidance recommended that SGLT 2s be available for this indication. Again, the economic modelling conducted was based on simulated changes in diabetes complications as a result of surrogate endpoints An application for monotherapy use of SGLT 2 inhibitors has to date not been considered by PHARMAC.

4. PHARMAC Cost-Utility Analysis

A Markov model cost utility analysis (CUA) was undertaken to estimate the cost effectiveness of SGLT-2 inhibitors for T2DM with high cardiovascular disease risk.

4.1 Scope of Analysis

The analysis was undertaken from the perspective of the funder, with regards to PHARMAC's Factors for Consideration.

4.1.1 Target Population

The target population for this analysis was defined as people with T2DM with high CVD risk (see Special Authority outlined in Table 1).

4.1.2 Intervention

Following clinical advice that SGLT-2 inhibitors are likely to have the same or similar therapeutic effect, it was decided by PHARMAC staff at Hot Topic July 2019 (zA195267) that the SGLT-2 inhibitor model will be based on Empagliflozin.

Empagliflozin (10mg or 25mg) is a tablet that is taken once daily in addition to best standard of care for T2DM and cardiovascular disease.

4.1.3 Comparator

The comparator(s) used in the analysis was best standard of care for T2DM and cardiovascular disease (i.e effectively placebo).

4.2 Model Structure

A Markov model was constructed to model the different treatment strategies.

4.2.1 Time Horizon

The time-horizon of the CUA was 10-years. Each Markov cycle was monthly.

The time-horizon of the CUA is noted to be shorter than the duration of benefit that could be expected from treatment with a SGLT 2 inhibitor. However, PHARMAC staff decided at the Hot Topic on 29th July 2019 (zA195267) that a 10-year time horizon was an appropriate time horizon to extrapolate the currently available data regarding cardiovascular disease outcomes. PHARMAC staff considered that the influence of other factors beyond this time horizon, including the effects of aging and the burden of comorbidities, were likely to confound the ongoing clinical effect of the intervention Evidence on the efficacy of SGLT 2 inhibitors over a longer time-horizon has not been reviewed by PTAC or its Subcommittees. A sensitivity analysis was conducted using a 15 year time horizon.

All costs and benefits were discounted at 3.5%.

4.2.2 Model Structure

The Markov model health states and events that could occur per Markov cycle relative to the health state are outlined in Table 3 and illustrated in Figure 2.

The proportion of the population starting the model at each health state at baseline was informed by baseline characteristics of the EMPA Reg trial (Zinman et al, 2015) The trial excluded those with an eGFR low enough to be on kidney dialysis, so none of the modelled population started the model in the renal dialysis states In the trial, 59% had an albumin to creatine ratio (ACR) of <30mg, consistent with no macroalbuminuria and 48% were on insulin. The resulting population split is outlined in Table 3 below

Table 3: Model health states and baseline model population.

Health State	Proportion of model population at baseline	Possible events per cycle
T2DM no insulin	31% (52% of 59%)	• Die • Have a heart failure hospitalisation • Initiate insulin • Start renal dialysis • Develop macroalbuminuria
T2DM on insulin	28% (48% of 59%)	• Die • Have a heart failure hospitalisation • Start renal dialysis • Develop macroalbuminuria
T2DM no insulin with macroalbuminuria	21% (52% of 41%)	• Die • Have a heart failure hospitalisation • Initiate insulin • Start renal dialysis
T2DM on insulin with macroalbuminuria	20% (48% of 41%)	• Die • Have a heart failure hospitalisation • Start renal dialysis
T2DM no insulin on renal dialysis	0	• Die • Have a heart failure hospitalisation • Initiate insulin
T2Dm on insulin on renal dialysis	0	• Die • Have a heart failure hospitalisation

People in the health state 'T2DM no insulin' within each cycle had a probability of having a heart failure hospitalisation, initiating insulin, starting renal dialysis or if not starting on renal dialysis progressing to macroalbuminuria The events that occurred within the cycle determined progression to other health states. For example, people in the health state 'T2DM no insulin' who within the cycle had a heart failure hospitalisation, initiated insulin but did not progress to renal dialysis but did develop macroalbuminuria would then move to the health state 'T2DM on insulin with macroalbuminuria'

The probability of modelled events (i.e. all cause death, heart failure hospitalisation, insulin initiation, progression to macroalbuminuria and renal dialysis) was the same in each health state (i.e. events were considered to be independent). The purpose of the different health states was to better reflect quality of life and costs changes between different subsets of the population.

A branch of the Markov model is included on the following page (Figure 2):

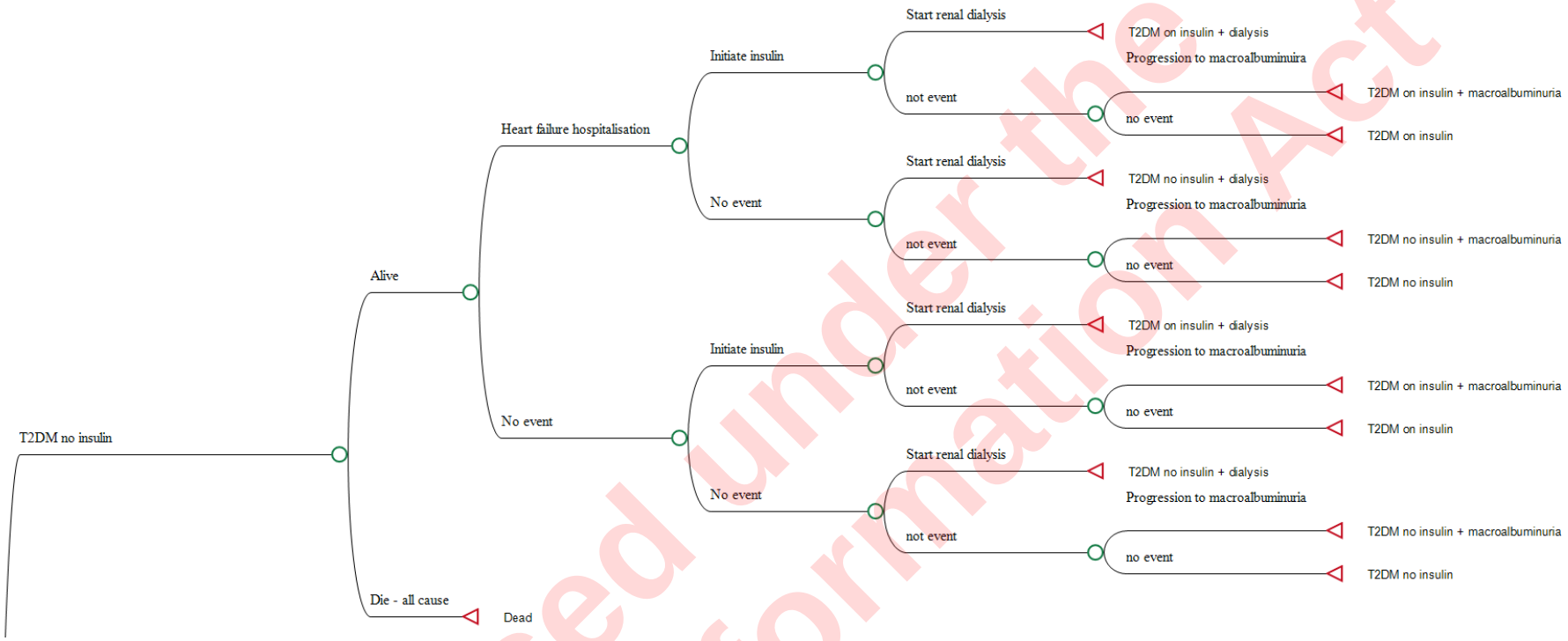


Figure 2: Section of Markov model

Note: This is a section of the Markov model from one health state only. Some branches are missing from subsequent health states where the modelled event has already occurred. I.e. in the health state T2DM on insulin and renal dialysis there is no probability of initiating insulin or initiating renal dialysis.

4.3 Transformation and Extrapolation of Clinical Evidence

The clinical effect of empagliflozin was informed by the results of the EMPA REG trial The primary publication by Zinman et al, 2015 and the renal outcomes by Wanner et al, 2016. Only outcomes where the difference between the intervention and comparator were statistically significant were considered for inclusion in the CUA analysis. Composite outcome measures were also excluded For empagliflozin in the EMPA REG trial the statistically significant endpoints included in the model were:

- Death
  - All cause
  - CVD death
- Heart failure (HF) hospitalisation
- Renal outcomes
  - Progression to macroalbuminuria
  - Initiation of renal replacement therapy
  - Doubling of serum creatine + eGFR ≤45ml/min/1.73m^2

As CVD death is included in the measure of all-cause death, only all-cause death was modelled The variable, doubling serum creatine levels, was not specifically modelled due to uncertainty with respect to the outcomes impact on HR QOL and heathy system costs in addition to the risk of double counting costs or benefits accounted in progression to macroalbuminuria and initiation of renal replacement therapy.

Table 4: Summary of statistically significant outcomes from Zinman et al, 2015.

Variable	Empagliflozin		Placebo	
	Incident rate (events per 1000 patient years) *	Incident rate (events per 1 patient year)	Incident rate (events per 1000 patient years) *	Incident rate (events per 1 patient year)
Death from any cause	19.4	0.019	28.6	0.029
Heart failure hospitalisation	9.4	0.009	14.5	0.015
Initiation of renal replacement therapy	1 0	0 001	2 1	0 002
Progression to macroalbuminuria	41.8	0.0418	64.9	0.0649
* Source: Zinman et al, 2015 + Wanner et al, 2016				

4.3.1 Probability of initiating insulin

The T2DM treatment paradigm outlined in 'Guidance on the Management of type 2 diabetes' published by the Ministry of Health advises that if HbA1c is not within the target range of 50-55mmonl/L after 3 months, the treatment regimen should be intensified In the EMPAG REG trial, despite a small reduction in HbA1c post initiation of therapy, the average HbA1c after 206 weeks was still 7.5-8%.

In the absence of information regarding a delay in time to insulin specifically to SGLT2 inhibitors, the base case of the model conservatively assumes that the addition of additional oral therapy (i.e. adding another line of therapy) will at minimum delay the progression to insulin by 3 months compared to status quo To represent this, the base case assumes that all patients not on insulin in the comparator arm of the model (i.e. representing status quo)

initiate insulin at the start of the model while patients not on insulin the intervention arm or the model at baseline initiate insulin after 3-months The impact of a longer potential delay in initiating insulin will be considered in the model sensitivity analyses.

4.4 Health Related Quality of Life

Several studies that examined the health related quality of life for people with T2DM were identified by PHARMAC staff

- **Zhang et al, 2012** a multi centre observation study titled 'Translating Research into Action for Diabetes' which recorded EQ 5D values for 7,327 individuals with T2DM

- **Sullivan et al, 2016** a study of 20,705 individuals with diabetes (type 1 and 2 combined) The original questionnaire was completed in the United States, but United Kingdom utility preferences were applied.

- **Beaudet et al, 2014** a systematic literature search of T1DM and T2DM related complications 19 studies were included, the majority were conducted in the United Kingdom. The study presents a range of values as well as a 'preferred' utility data set for use in economic modelling Many data inputs in the preferred data set were values determined by Clarke et al in 2002 for the UKPDS model.

The utility weights for T2DM and its complications from the three studies above as well as the utility weights from the Global Burden of Disease Study 2017 are presented in Table 5 below

Table 5: Summary of health utility values from various publications

Health state	Zhang et al. 2012	Sullivan et al 2016	Beaudet et al 2014	GPD 2017 Utility weight (Disability weight)
Source	Link	Link	Link	Link
Uncomplicated T2DM	0.80	0.719	0.785	0.95 (0.049)
End stage renal disease on dialysis	0 68	0 681 (dialysis not specified	0 621 (Haemodialysis) 0.581 (CAPD) 0 60 Average**	0 43 (0 571)
Cardiovascular diseases*	0 68-0.78	0 65-0 68	0 62 0 73	Large range depending on severity Not specific for diabetes population
Diabetes – oral medication	0.82	n/a	n/a	n/a
Diabetes insulin	0 75	n/a	n/a	n/a
* range includes utilities values for myocardial infarction, ischemic heart disease, congestive heart failure, stroke, peripheral vascular disease, transient ischemic attack ** weighted average on proportion of people on either dialysis type in New Zealand (see section 4.5.3 below)				

The majority of health state utility values used in the model were informed by the systematic review conducted by Beaudet et al 2014 and their recommended utility value set for diabetes

modelling. Beaudet et al was chosen due to the place of systematic reviews in the hierarchy of evidence and the fact that the majority of the utilities were derived using the United Kingdom value set which was considered by PHARMAC staff to be boarder generalisable to New Zealand (Hot topic August 2019 zA195270).

Utility of T2DM with established CVD disease

The base case utility value for patients not on insulin with T2DM and established CVD is 0 73 This value represents the upper range of utility values presented for a variety of cardiovascular diseases within T2DM patient and appears reasonable given other published literature and the utilities estimated by PHARMAC staff using the New Zealand preference weights.

Utility weight of patients on dialysis

The utility weight for a patient on dialysis was determined to be 0.60 after weighting to reflect the proportion of patients in New Zealand on either haemodialysis or CAPD dialysis. For further information, see section 4.5.3 on the cost of dialysis.

Utility weight of patients on insulin

A utility decrement for patients on insulin compared to patients on oral therapies only was included in the model as informed by Zhang et al (-0.07). This decrement was intended to represent the health related quality of life associated with using regular injection based therapies and blood glucose monitoring as well as the fear associated with progressing disease The limited sensitivity of the EQ 5D measure to pick up the difference associated with progression to insulin was a noted issue in the literature and by PHARMAC staff. The sensitivity of the model to this decrement was investigated in the sensitivity analyses. The decrement was not applied to states where patients were on dialysis as it was assumed that this was captured in the utility value of being on dialysis.

Utility weight of patients hospitalised for heart failure

The one off decrement of patients who have a heart failure hospitalisation in the model was informed by Ambrosy et al, 2015. Ambrosy et al, 2015 used EQ 5D to measure patients at admission, during admission and at discharge of a hospitalisation due to acute heart failure (ASCEND-HF trial). The study included 6,943 patients who had an average utility at admission of 0 56 which increased to 0.67 at 24hr, 0 79 at discharge and 0 78 at day 30 The difference in day 30 and at point of admission was used to inform the one-off utility decrement of a heart failure hospitalisation (0 20). The disutility was only applied for one month The disutility of patients who experienced a heart failure hospitalisation aligns with a previous analysis done by PHARMAC staff for the pharmaceutical sacubitril and valsartan for heart failure. It was noted that this was a PHARMAC estimate (objective link A1095176)

The utility weights used in the model were discussed and considered appropriate by PHARMAC staff at the second hot topic presentation in August 2019 (zA195270)

Table 6 Utility values estimated by PHARMAC staff using NZ-Tariffs

Health State	Utility	EQ-5D	Health state description
T2DM – oral therapies only	0.704-1 (average 0 85)	1,1,1,1,1	no problems walking; no problems with self-care; no problems with performing usual activities; no pain or discomfort; not anxious or depressed
		1,1,1,1,2	no problems walking; no problems with self care; no problems with performing usual activities; no pain or discomfort; moderately anxious or depressed.
T2DM oral +insulin	0.624	1,1,1,2,2	no problems walking; no problems with self-care; no problems with performing usual activities; moderate pain or discomfort; moderately anxious or depressed.
T2DM with end stage kidney disease on dialysis	0 464	2,2,2,2,2	some problems walking about; some problems washing or dressing self; some problems with performing usual activities; moderate pain or discomfort; moderately anxious or depressed.

Table 7 Utility values used in model

Heart state/event	Utility value
T2DM no insulin	0.73
T2DM on insulin	0 66
T2DM no insulin with macroalbuminuria	0 73
T2DM on insulin with macroalbuminuria	0.66
T2DM no insulin on renal dialysis	0.60
T2Dm on insulin on renal dialysis	0.60
T2DM with Heart failure	0 20/12

4.5 Costs

4.5.1 Pharmaceutical Cost

Empagliflozin

Empagliflozin is a once daily tablet of either 10mg or 25mg and comes in packs of 30 tablet The pharmaceutical cost of empagliflozin is outlined in Table 8 below.

Table 8 Pharmaceutical Cost – Empagliflozin

Form, strength and pack size	10mg or 25mg tablets, packs of 30
List price per pack*	$58.56
Price after rebate per pack*	Withhel
Dose per day	25mg or 10mg once daily
Cost per dose	Withh
Cost per month (30 days)	Withhel

Supplier offer Jan 2018

Insulin

The model considered both a delay in the initiation of insulin (see section *4.5.3*) for those who were not already on insulin and a reduced dosage of insulin once on insulin for the use of an SGLT-2 inhibitor.

Cost per insulin unit

The cost per unit of insulin differs between insulin products. To reflect this, the cost of insulin in the model was weighted by the market share of insulin glargine to insulin isophane. Insulin glargine and insulin isophane are the two most commonly dispensed insulins for T2DM in New Zealand. In 2018, approximately 14,000 (25%) people were dispensed insulin isophane and 42,000 (75%) were dispensed insulin glargine (source: PHARMhouse). The weighted cost per unit of insulin (including confidential rebate) was Withhel (see Table 9)

Number of units

The average dose of insulin for the placebo arm of the model (not on a SGLT 2 inhibitor) was informed by the median daily international units of insulin used at baseline in the EMPAG reg trial (53 units (average of placebo and intervention arm of the EMPAG reg trial))

The average dose of insulin for the intervention arm of the model (on a SGLT 2 inhibitor) was determined by subtracting the mean change from placebo from the early empagliflozin clinical trial (Rosenstock et al 2015) from the median daily dose described above from the EMPAG-reg trial. The difference in study population between Rosenstock et al 2015 and Zinman et al (primarily CVD risk) was noted by PHARMAC staff at the hot topic (zA195270) Staff noted that in the absence of other information, this was a reasonable approximation of the insulin dose reduction that could be expected while on a SGLT 2 inhibitor. The impact of this assessment was tested in the sensitivity analysis

Table 9: Pharmaceutical Cost Insulin glargine/Insulin isophane

Form, strength and pack size	Insulin glargine: 5x3ml pen, 100 units per ml Insulin isophane: 5x3ml pen, 100 units per ml
Price per pack (before rebate)	Insulin glargine $95 50 Insulin isophane: $29.86
Weighted cost per international insulin unit (rebate included)	Withh
No SGLT 2 inhibitor + insulin	
Dose per day	53 units (source: baseline daily IU of insulin EMPA reg trial)
Cost per dose	Withh
Cost per month	Withhel
SGLT 2 inhibitor + insulin	
Dose per day	47 units (source: baseline daily IU of insulin EMPA-reg trial change in IU from Rosenstock et al 2015)
Cost per dose	Withh
Cost per month	Withhel

Insulin test strips

It was assumed in the model that people on insulin would require two blood glucose tests a day on average. This was a conservative approximation based on PHARMAC dispensing data. The model sensitivity to this assumption was tested in the sensitivity analysis. The cost of test strips is broken down in Table 10 below

Table 10: Pharmaceutical Cost – Blood glucose diagnostic test strip

Form, strength and pack size	Packs of 50 test strips
Price per pack	$10.56
Rebated price per pack (Confidential)	Withh
Dose per day	2 test a day
Cost per test	Withh
Cost per day (2 tests)	Withhe
Cost per month	Withh

Insulin needles

The model includes the cost of one insulin needle per day This assumption was based on the Ministry of Health Guidance on the Management of Type 2 Diabetes 2011 which recommended T2DM patients on insulin have once daily insulin isophane. This assumption also concurs with the most commonly dispensed insulin formulations for this patient group (insulin isophane and glargine both long acting, once daily formulations) The model sensitivity to this assumption was tested in the sensitivity analysis

Form, strength and pack size	Packs of 100 needles
Price per pack	$10.50
Dose per day	1 per day
Cost per needle	$0.1050
Cost per month	$3.04

4.5.2 Pharmacy margin + pharmacy fee

The pharmacy margin for a pharmaceutical with a list price per pack under $150 is 3% per pack. In addition, each pharmacy dispensing incurs a cost of $5.44 as a pharmacy handling

and service fee. The pharmacy margin and handling fee for the pharmaceutical items included in the model is outlined in Table 11 below.

Table 11: Pharmacy fees empagliflozin

	Empagliflozin	Insulin	Test scripts	Needles
Pharmacy mark up per pack	3%	3%	3%	3%
List price per pack	$58 56	$79 09*	$10 56	$10 50
Pharmacy mark up per pack	$1.76	$2.37	$0.32	$0.32
Pharmacy mark up per month	$1.76	$2.37**	$0.43***	$0.32
Pharmacy handling and service fee per dispensing	$5.44	$5.44	$5.44	$5.44
Pharmacy handling and service fee per month#	$1.81	$1.81	$1.81	$1.81
* list price weighted by the market share of insulin glargine to insulin isophane (see section 4.5.1 for detail) **Assumes that on average patients require 50 units a day or 1500 units per 30-day period equivalent to one 'pack' of insulin glargine per 30-day period ***Assuming 2 tests per day for a 90-day period (180 test) 4 packs of 50 will be dispensed # Assuming 4 90 day dispensing per year				

4.5.3 Co-payments

Empagliflozin if funded would likely be a community pharmaceutical with a 90-day prescription period. As such, the model considers the annual cost of empagliflozin to include the cost of four prescriptions ($5.40).

4 5 4 Health Sector Costs

Table 12 summaries the health care costs included in the model. Each cost is described in turn below

Table 12: Summary of Health Sector Costs

Event	Cost ($)	Unit
Heart failure hospitalisation	$5,598	Per event
Renal Dialysis initiation	$9,060	One off
Renal Dialysis ongoing	$2,484	Monthly
Renal Dialysis monitoring	$653	Annually
Macroalbuminuria initiation	$765	One off
Macroalbuminuria ongoing	$406	Annually
Insulin initiation	$589	One off
Source: multiple (see relevant explanation below)		

Cost of heart failure hospitalisation

The transitional cost associated with a heart failure hospitalisation event was calculated by taking the weighted average of the average cost of admission for the two, heart failure DRGS

- Heart failure and shock w catastrophic CC (DRG F62A)
- Heart failure and shock w/o catastrophic CC (DRG62B)

The weighting was done based on the number of dischargers associated with each DRG The resulting average cost of a heart failure hospitalisation was $5,598 The average length of stay for heart failure for these two DRGs respectively was 8 and 5 days A variety of scenario analysis in which the cost of a heart failure hospitalisation was increased were conducted These scenario analyses reflect that the modelled population would potential have a more severe HF admission duration due to having a greater risk profile than the average population.

Cost of renal dialysis

Patients progressing to renal dialysis may receive haemodialysis or continuous ambulatory peritoneal dialysis (CAPD) A point prevalence survey conducted by the Australia New Zealand Dialysis and Transplant registry (source: ANZDATA 41st Annual report 2018) reported that on 31st of December 2017:

- 2427 people in New Zealand were receiving CAPD dialysis
    - 66% of whom were receiving dialysis at home (1,602 people).
- 1913 people in New Zealand were on haemodialysis
    - 23% of whom were receiving dialysis at home (440 people)

Of the population of patients on home dialysis (2,041 people), 78% were on CAPD, 22% were on haemodialysis. These proportions informed the weighting of the average cost of dialysis

Table 13: Cost of home-based renal dialysis

Item	Cost	Frequency
CAPD training	$3,040	per patient one off
Recurrent home based CAPD	$2,258	per patient per month
Haemodialysis training	$16,722	per patient one off
Recurrent home based Haemodialysis	$2,772	per patient per month
Source: PHARMAC cost-resource manual 2018.		

Table 14: Weighted cost of renal dialysis procedures

Item	Cost
Weighted average cost of home dialysis initiation	$6,050
Weighted average cost of recurrent home dialysis (per month)	$2,371
Source: calculated using PHARMAC cost resource manual costs and proportion of patients receiving either dialysis method at home in NZ from ANZDATA	

Cost of monitoring of dialysis

The model accounts for the bi-annually cost of two nephrology visits (Renal Medicine - $653 annually - $54 a month on average) The impact of the cost of monitoring patients on dialysis was considered in the sensitivity analyses

The limitation of not including those who are on dialysis for a short duration before having a kidney transplant was acknowledged by PHARMAC staff.

Cost of initiating insulin

The health sector cost of initiating insulin was informed by the Ministry of Health Guidance on the Management of Type 2 Diabetes 2011, which recommends blood glucose levels be reviewed every 2-4 days until blood glucose becomes stable and an appropriate dosing regimen is decided upon Once blood glucose levels are stable on insulin, re review is recommended every 3 6 months in combination with monitoring changes in HbA1c levels.

The model includes a one off cost of initiating insulin of four GP visits and an attendance at a Diabetes Education and Care centre No ongoing cost of insulin therapy was accounted for in the model as it was assumed that ongoing review and monitoring occurs at routine appointments that occur regardless of insulin or SGLT 2 inhibtor therapy. The sensitivity of the cost of initiating insulin was considered in the sensitivity analyses.

Table 15: Cost of initiating insulin

Item	Cost
Diabetes Education and Care (Diabetes education and care by multi-disciplinary teams in hospital or community based setting)	$269.03
GP visit	$80
Total	$589
Source: PHARMAC cost resource manual 2018	

Cost of progression to macroalbuminuria

Best practice guidelines published by BPAC NZ in February 2015 (The detection and management of patients with chronic kidney disease in primary consensus statement), suggest kidney function tests should be a part of the regular CVD and diabetes assessment. Following a kidney functioning test result indicative of macroalbuminuria, a referral to nephrology and a renal ultra-sound is recommended in addition to some blood work. Upon transition to macroalbuminuria the model attributes a one off transitional cost of a nephrologist attendance and an abdominal ultrasound (proxy for renal ultrasound as no specific price was found) (See Table 16 for costs).

Cost of macroalbuminuria

Subsequently, patients with macroalbuminuria in the model who are not yet on kidney dialysis are assumed to have an annual nephrologist visit and an additional GP visit (See Table 16 for costs)

Table 16: Costs associated with macroalbuminuria

Item	Cost	Frequency
First attendance nephrologist	$551.71	Per attendance
Subsequent attendance nephrologist	$326.32	Per attendance
Abdominal ultrasound	$213	Per ultrasound
GP visit	$80	
Source: PHARMAC cost resource manual 2018		

Routine GP visits

The cost of a general practice visit where the prescription would be given to the patient was not considered in the model because it was assumed that the prescription would occur at a routine appointment and that these routine appointments would be occurring with similar frequency between the empagliflozin and best standard of care arm of the model given the high health need of study population. (That is, it was assumed that this cohort of patients would be regularly visiting a GP to manage and receive the scripts for their diabetes and CVD).

Adverse events

The cost, health-related quality of life or discontinuation of therapy of patients who experience adverse events was not considered in the model as the incremental difference between the two therapies and the relative cost of treating the most frequently occurring adverse events (e.g. urinary tract infections and genital infections) was considered to be immaterial (Hot topic July 2019 (zA195267))

4.6 Cost-Effectiveness Results

The incremental cost is estimated to be Withheld with a QALY gain of 0 27 The estimated QALYs per $1million is Withheld under (cost per QALY of Withheld). This is shown in the table below

Table 17: Cost-Effectiveness Results

	SGLT-2 inhibitor (Empagliflozin)	Placebo (BSC)	Incremental
QALYs	5 11	4 84	0.27
Cost	Withheld	Withhe	Withhe
QALYs per $1m		-	Wi

4.8 Summary of Overall Cost-Effectiveness

The incremental cost is estimated to be Withheld with a QALY gain of 0 27 The estimated QALYs per $1million is Withheld under (cost per QALY of Withheld). The likely cost-effectiveness range (Withheld) incorporates likely variations in the probabilities of death, heart failure hospitalisation and progression to macroalbuminuria as well as variation in the utility values used, the cost of macroalbuminuria and heart failure hospitalisation, a 24 months delay in insulin initiation. The possible cost-effectiveness range (Withheld) incorporates the possibility of no benefit from insulin (usage and delay to progression), up to 35 months delay in progression to insulin and a commercial offer received from a supplier of an agent within the class

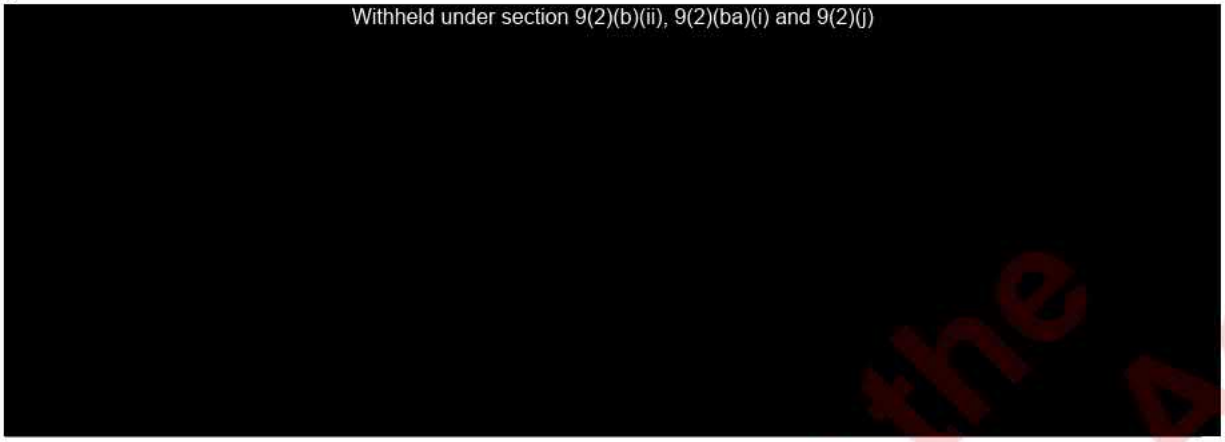
Table 18 Sensitivity analyses

Sensitivity analysis	Additional description	Incremental Cost	Incremental QALY	$/QALY	QALY/ $m
Base-case		Withhel	0 27	Withheld	Withhel
General					
Time horizon (BC 10 years)	5 years	Withheld under	0 10	Withheld under	Withheld under
	15-years	Withhel	0.47	Withhel	Withhel
Discount rate (BC 3 5%)	0%	Withhel	0 33	Withhel	Withhel
	5%	Withhel	0.24	Withheld	Withhel
Proportion of patients in health states at model baseline	75% no insulin, 12% insulin, 9% no insulin + macroalbuminuria, 1% insulin + macroalbuminuria, 3% no insulin + dialysis, 0% insulin + dialysis (CVD risk>15%)	Withhel	0.27	Withheld	Withhel
Probabilities					
Probability of death SGLT	Decrease the difference between SGLT-2 inhibitor and placebo by 50% (+0 005)	Withhel	0.15	Withheld	Withhel
	Increases the difference between SGLT-2 inhibitor and placebo by 50% (-0.005)	Withhel	0 38	Withheld	Withhel
Probability of HF	Decrease the difference between SGLT-2 inhibitor and placebo by 50% (+0 003)	Withhel	0.26	Withheld	Withhel
	Increases the difference between SGLT-2 inhibitor and placebo by 50% (-0.003)	Withhel	0 27	Withhel	Withhel
Probability of starting dialysis	Annual rate of starting dialysis with SGLT-2 inhibitor 0.0015 (BC 0.001)	Withheld under	0.27	Withheld under	Withheld under
	annual rate of starting dialysis with SGLT-2 inhibitor 0 0005 (BC 0 001)	Withheld under	0 27	Withheld under	Withheld under
Probability of progression to macroalbuminuria	Decrease the difference between SGLT-2 inhibitor and placebo by 50% (-0.003)	Withhel	0.27	Withheld	Withhel
	Increases the difference between SGLT-2 inhibitor and placebo by 50% (+0.003)	Withhel	0.27	Withheld	Withhel
Utilities					
Utility T2DM with CVD (BC 0 73)	Utility + 0 1	Withhel	0 28	Withheld	Withhel
	Utility - 0.1	Withhel	0.25	Withheld	Withhel
Utility T2DM with CVD + insulin (BC 0 66)	Decrease the utility decrement between insulin and not on insulin by 50% (-0 695)	Withhel	0 27	Withheld	Withhel
	Increase the utility decrement between insulin and not on insulin by 50% (+0.625)	Withhel	0.26	Withheld	Withhel
Scenario analysis utilities	Utility on insulin same as not on insulin	Withheld under	0.28	Withheld under	Withheld under
Utility T2DM on dialysis (BC 0.60)	Utility + 0 1	Withhel	0 26	Withheld	Withhel
	Utility - 0.1	Withhel	0.27	Withheld	Withhel
Utility decrement for HFH (BC -0.20 for a month)	Utility *1 5	Withhel	0 28	Withheld	Withhel
	Utility *0.5	Withhel	0.25	Withheld	Withhel
Costs					
Cost of empagliflozin (base-case Withh per tab)	Withh per tab	Withhel	0.27	Withheld	Withhel
	Withh per tab	Withhel	0 27	Withheld	Withhel
	Withh per tab	Withhel	0.27	Withheld	Withhel

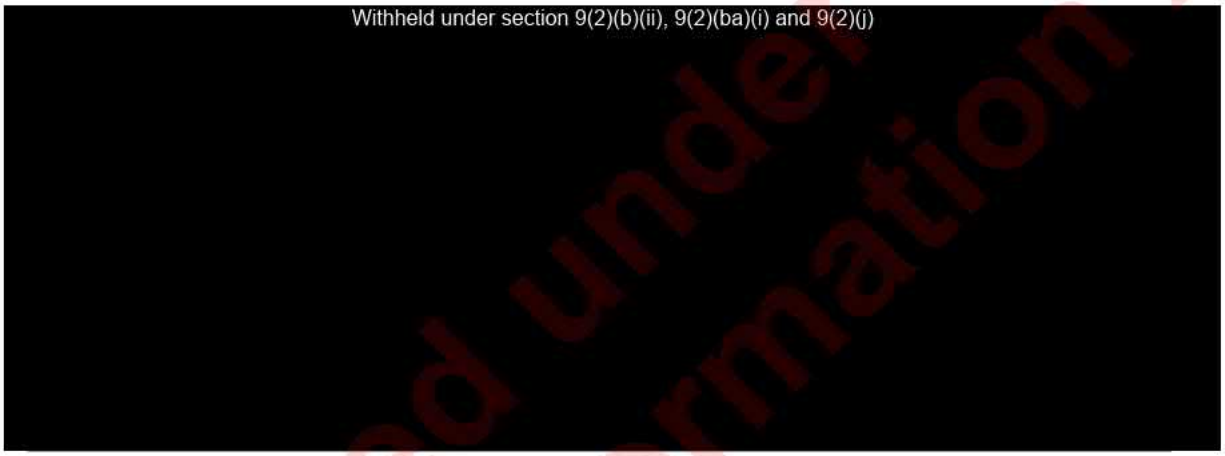
Sensitivity analysis	Additional description	Incremental Cost	Incremental QALY	$/QALY	QALY/ $m
	Withh per tab	Withhel	0.27	Withheld	Withhel
	Withh per tab	Withhel	0 27	Withheld	Withhel
	Withh per tab	Withhel	0 27	Withheld	Withhel
	Withh per tab	Withhel	0.27	Withheld	Withhel
Commercial offer received assumes the agent is open listed	Withheld under section 9(2)(b)(ii),	Withhel	0 27	Withheld	Withhel
Increased cost of insulin needles and test strips	Cost of insulin test strips and needles x2	Withheld under	0.27	Withheld under	Withheld
Cost of initiating insulin (BC $589)	Base case * 4	Withheld under	0.27	Withheld under	Withheld
Cost of HFH ($5598 BC)	Base case * 2	Withhel	0.27	Withheld	Withhel
	Base case * 4	Withhel	0.27	Withheld	Withhel
Insulin assumptions					
Insulin	Placebo and SGLT-2 inhibitor use double number of insulin units a day	Withheld under	0.27	Withheld under	Withheld
	Placebo and SGLT-2 inhibitor use triple number of insulin units a day	Withheld under	0.27	Withheld under	Withheld
	No difference in the insulin units used with SGLT 2 inhibitor or placebo	Withhel	0.27	Withheld	Withhel
	Difference in daily insulin units 1.5* base-case (BC SGLT 2 inhibitor -6 units, analysis SGLT-2 inhibitor -9 units)	Withhel	0 27	Withheld	Withhel
	Difference in daily insulin units double base-case (BC SGLT-2 inhibitor 6 units, analysis SGLT-2 inhibitor -12 units)	Withhel	0.27	Withheld	Withhel
	Remove insulin (no progression to insulin, no reduction in insulin units on therapy)	Withhel	0.17	Withheld	Withhel
Time to progression to insulin (BC 3 months)	6 months	Withhel	0 28	Withheld	Withhel
	12 months	Withhel	0.29	Withheld	Withhel
	24 months	Withhel	0 33	Withheld	Withhel
	36 months	Withhel	0.36	Withheld	Withhel
Cost of microalbuminuria	Initiation and ongoing costs *4	Withhel	0 27	Withheld	Withhel
Cost of monitoring dialysis	Monitoring cost *4	Withheld under	0.27	Withheld under	Withheld

Figure 3: Graph of various sensitivity analysis

A



B.



Graph A shows sensitivity analysis for time horizon, probabilities, utilities and costs **Graph B** shows sensitivity analysis for insulin assumptions

The red vertical line indicates the base-case estimate

Grey box represents the likely range, green box represents the possible range.

Note: columns with pattern represent values with QALY/$million greater than Wit

TH: time horizon, HF: heart failure, diff.incr: difference between placebo and intervention increase, diff.decr: difference between placebo and intervention decreased, MA: macroalbuminuria, HFH: heart failure hospitalisation

5. Budget Impact Analysis

5.1 Summary of Budget Impact

- The proportion of people with T2DM who have a CVD risk score of greater than 15% was determined from data received from Auckland Universities PREDICT project (confidential) Applying this proportion to the number of people with type two diabetics in New Zealand resulted in an eligible population of Withheld
- Population of 2% annually was considered.
- Two cost offsets where considered in the BIA: cost offset from a reduce use of metformin monotherapy and insulin
    - There are two formulation of empagliflozin or SGLT-2 inhibitor that would be listed if funded: empagliflozin monotherapy and empagliflozin in combination with metformin (single-pill formulation). The price for each formulation is the same, therefore patients who use the combination product and therefore no longer need to take metformin monotherapy incur a saving to the combined pharmaceutical budget. The proportion of the eligible population who would use the combination formulation compared to the monotherapy formulation was informed by the split between the two formulations for vildagliptin in 2018 (63% monotherapy and 37% combination)
    - As described for the CUA above, being on a SGLT 2 inhibitor was assumed to result in a reducing of 6 insulin units a day. This was included in the BIA for the Withh of the population who would be on insulin (PREDICT data set). The cost of delaying the progression to insulin was not included due to the uncertainty in this and the fact that it is just delaying a cost rather than mitigating it. The cost of insulin needles was also not included as it was considered negligible
- The DHB line of the BIA considers the net change in pharmacy mark ups (SGLT 2 inhibitors and metformin) and patient-co-payments for SGLT-2 inhibitor (increase for SGLT-2 inhibitors minus those on the combination product who would not experience an increase in co-payments). The pharmacy mark-up cost of insulin were not included as it was immaterial.
- Uptake was assumed to increase linearly by month from the day of listing for 2 years until a steady state of 60% uptake was met (TGM opinion)
- All costs were as described in the CUA above.
- BIA objective link - A1305215

Year	2020	2021	2022	2023	2024	5-Year NPV (8%)
CPB costs (Millions)	Withh eld	Withhel d under	Withhel d under	Withhel d under	Withhel d under	Withhel d under
CPB savings (Millions)	Withh eld	Withhel d under	Withhel d under	Withhel d under	Withhel d under	Withhel d under
CPB net (Millions)	Withh eld	Withhel d under	Withhel d under	Withhel d under	Withhel d under	Withhel d under
DHB (Millions)	$0.28	$0.81	$1.07	$1.09	$1.11	$3.63

5.2 Summary of Budget Impact

The net cost to the community/hospital pharmaceutical schedule is expected to be Withhel Withhel in year 1 with a 5-year net present value (NPV) of Withheld under . The net cost to DHBs is expected to be $0.28 million in year 1 with a 5 year NPV of $3.63 million