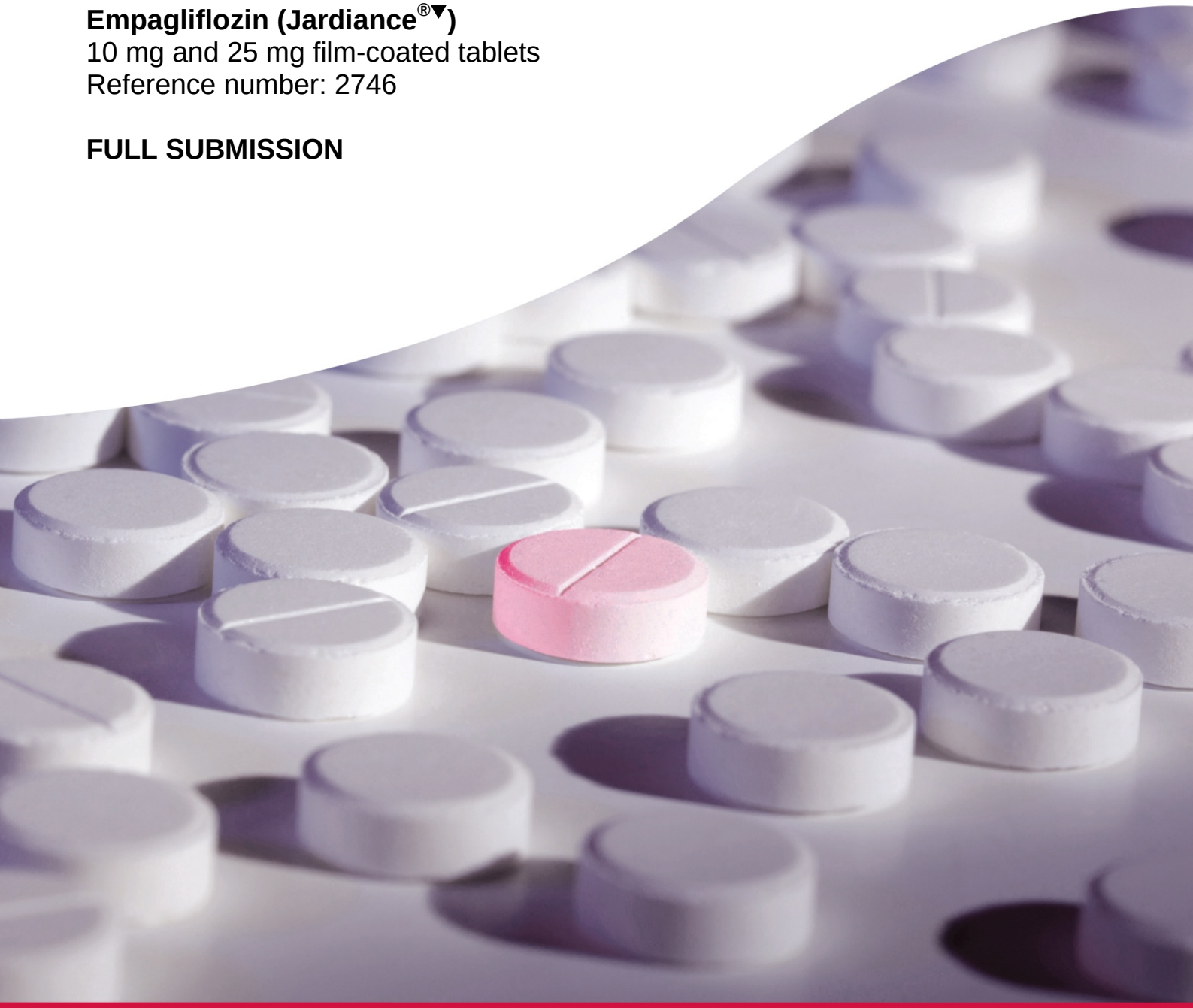
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Empagliflozin (Jardiance®▼)
10 mg and 25 mg film-coated tablets
Reference number: 2746

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

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AWMSG Secretariat Assessment Report
Empagliflozin (Jardiance®▼) 10 mg and 25 mg film-coated tablets

This assessment report is based on evidence submitted by Boehringer Ingelheim Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Empagliflozin (Jardiance®▼) for the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as: Monotherapy. When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2,3].
Dosing	The recommended starting dose is 10 mg empagliflozin once daily. In patients tolerating empagliflozin 10 mg once daily who have an estimated glomerular filtration rate (eGFR) of ≥ 60 ml/min/1.73 m^2 and need tighter glycaemic control, the dose can be increased to a maximum of 25 mg once daily[2,3].
Marketing authorisation date	22 May 2014[2,3]

2.0 DECISION CONTEXT

2.1 Background

Type 2 diabetes mellitus (T2DM) is associated with increased macrovascular risk including cardiovascular disease and stroke, and microvascular complications such as retinopathy, neuropathy and nephropathy[4]. In people with T2DM the beta cells are not able to produce enough insulin for the body's needs. The majority of people with T2DM also have some degree of insulin resistance, where the cells in the body are not able to respond to the insulin that is produced[5]. Diabetes UK data indicates that the prevalence of diabetes in Wales is approximately 6.7%, of which 90% (187,362 people) have T2DM[1,6].

National Institute for Health and Care Excellence (NICE) Clinical Guidance (CG) 87 recommends metformin as first-line treatment in patients with glycosylated haemoglobin (HbA_{1c}) ≥ 6.5% (48 mmol/mol, see Glossary) after trial of lifestyle interventions[4,7]. The sulfonylureas can be considered an alternative to metformin if the patient is not overweight or metformin is not tolerated or contraindicated[4,7]. NICE Technology Appraisal (TA) 336 recommends empagliflozin for T2DM when taken in combination with metformin if the patient cannot take sulfonylurea or is at significant risk of hypoglycaemia. If the patient needs to take three antidiabetic medicines empagliflozin may be used with metformin and a sulfonylurea or a thiazolidinedione. Empagliflozin is also recommended for treating T2DM when taken with insulin with or without other antidiabetic medicines.

Empagliflozin is a sodium-dependent glucose co-transporter 2 (SGLT-2) inhibitor[8]. SGLT-2 proteins control renal reabsorption of glucose thus SGLT-2 inhibitors promote increased glucose excretion and therefore a reduction in blood glucose levels. In addition SGLT-2 inhibitors may have a low risk of hypoglycaemia, may reduce weight, and may reduce blood pressure[8].

This appraisal concerns the use of empagliflozin as a single agent (monotherapy) in patients intolerant to metformin[1]. Currently no SGLT-2 inhibitors are recommended for monotherapy in Wales. NICE is conducting a technology appraisal of SGLT-2 inhibitor monotherapies (canagliflozin, dapagliflozin and empagliflozin) for treating T2DM which is anticipated to be published in May 2016[9].

2.2 Comparators

The comparators included in the company submission include sulfonylureas, dipeptidylpeptidase-4 (DPP-4) inhibitors (e.g. linagliptin, sitagliptin, vildagliptin), thiazolidinedione (pioglitazone), and other SGLT-2 inhibitors (canagliflozin and dapagliflozin). With the exception of the SGLT-2 inhibitors, these medicines are all recommended as monotherapies for treating T2DM[1].

2.3 Guidance and related advice

- NICE TA (in development). Diabetes (type 2) - canagliflozin, dapagliflozin and empagliflozin (monotherapy) [ID756]. Anticipated publication May 2016[9].
- NICE TA336. Empagliflozin in combination therapy for treating type 2 diabetes. (2015)[10].
- NICE Pathway. Managing type 2 diabetes (2015)[7].
- Scottish Intercollegiate Guidelines Network. Management of diabetes. Guideline 116 (2010)[11].
- NICE. Type 2 diabetes: the management of type 2 diabetes. CG 87 (2009)[4].

The All Wales Medicines Strategy Group (AWMSG) has previously issued positive recommendations for the use of the following medicines for the treatment of patients with T2DM as monotherapies: linagliptin (Trajenta®▼)[12], vildagliptin (Galvus®)[13] and sitagliptin (Januvia®)[14] [in patients with renal impairment]. In the absence of a submission from the marketing authorisation holders dapagliflozin (Forxgia®)[15] and canagliflozin (Invokana®)[16] are not endorsed for use in Wales as monotherapies.

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of two phase III studies of patients with T2DM, 1245.20 and 1275.1, together with a network meta-analysis of studies obtained using data from a systematic literature search. In addition evidence from study 1240.31, a 52-week extension study of 1245.20 was submitted[1].

3.1 Study 1245.20

Study 1245.20 was a 24-week international phase III study in treatment-naive patients with T2DM (N = 986 enrolled) who experienced insufficient glycaemic control[1,17]. The majority of patients (n = 899) were randomised to receive double-blind treatment, however a small proportion (n = 87) with very poor glycaemic control (HbA_{1c} > 10%) were treated with open-label empagliflozin 25 mg once daily. Patients entering the randomised study were aged ≥ 18 years, had HbA_{1c} concentrations of 7.0–10.0%, and had received no antidiabetic treatment in the previous 12 weeks. Individuals with impaired renal function, defined as eGFR < 50 ml/min per 1.73 m^2 (or < 60 ml/min per 1.73 m^2 in China) were excluded from treatment.

The majority of patients entered a two-week placebo run-in period prior to being randomised 1:1:1:1 to one of four, once-daily, double-blind treatment regimens: empagliflozin 25 mg, empagliflozin 10 mg, sitagliptin 100 mg and placebo. In the full analysis set for the randomised patients in the double-blind study (n = 899) the proportions of Asian and White patients were 64.1% and 33.6% respectively. Results for the primary endpoint, change from baseline in HbA_{1c} after 24 weeks of treatment and key secondary endpoints at 24 weeks are shown in Table 1. The study was

powered to statistically compare the HbA_{1c} values of the active treatments versus placebo; comparison between the empagliflozin arms and the sitagliptin arm was not powered but was carried out as an exploratory analysis. Mean HbA_{1c} reductions did not differ significantly between treatment groups. Both doses of empagliflozin were associated with greater reductions in body weight, systolic blood pressure and diastolic blood pressure than sitagliptin[17].

Table 1. Endpoints for randomised patients in study 1245.20 at 24 weeks[17].

	Empagliflozin 25 mg n = 224	Empagliflozin 10 mg n = 224	Sitagliptin 100 mg n = 223
Primary endpoint			
Adjusted mean % change from baseline in HbA_{1c} (95% CI)	−0.78 (−0.88 to −0.67)	−0.66 (−0.76 to −0.56)	−0.66 (−0.76 to −0.56)
Difference in HbA_{1c} in % vs. sitagliptin	−0.12 (−0.26 to 0.03) p = 0.1060	0.00 (−0.15 to 0.14) p = 0.9697	-
Secondary endpoints			
Adjusted mean change from baseline in body weight in kg (95% CI)	−2.48 (−2.82 to −2.14)	−2.26 (−2.60 to −1.92)	0.18 (−0.16 to 0.52)
Difference in body weight in kg vs. sitagliptin (95% CI)	−2.67 (−3.15 to −2.18) p < 0.0001	−2.45 (−2.93 to −1.96) p < 0.0001	-
Adjusted mean change from baseline in systolic blood pressure, mm Hg (95% CI)	−3.7 (−5.3 to −2.1)	−2.9 (−4.5 to −1.3)	0.5 (−1.1 to 2.1)
Difference in systolic blood pressure in mm Hg vs. sitagliptin (95% CI)	−4.2 (−6.5 to −2.0) p = 0.0003	−3.4 (−5.7 to −1.2) p = 0.0031	-
Adjusted mean change from baseline in diastolic blood pressure, mm Hg (95% CI)	−1.9 (−2.9 to −1.0)	−1.0 (-2.0 to −0.1)	0.7 (−0.3 to 1.6)
Difference in diastolic blood pressure in mm Hg vs. sitagliptin (95% CI)	−2.6 (−3.9 to −1.3) p = 0.0001	−1.7 (−3.0 to −0.4) p = 0.0130	-
CI: confidence interval; HbA_{1c} values can also be expressed in mmol/mol (see Glossary).			

Results for the open–label 25 mg empagliflozin arm (n = 87) are not discussed in detail as these patients were not part of the randomised controlled study and were not therefore included in the same statistical analysis. However, results for the open–label arm were consistent with those observed in the main randomised study.

3.2 Study 1245.31

Study 1245.31 was a 52 week double-blind extension of 1245.20, with patients retained in the same study arms as in the randomised study[1,18]. Of 899 patients randomised to treatment in 1245.20, 615 continued into the extension study. Overall 354 patients discontinued the 24-week 1245.20 study or the 52-week extension study. Endpoints at the end of the full 76 weeks are given in Table 2 and show statistically significant difference in reduction of HbA_{1c} for empagliflozin 25 mg versus sitagliptin but only numerical improvement in for empagliflozin 10 mg versus sitagliptin. Changes in body weight and in blood pressures were statistically favourable to empagliflozin versus sitagliptin[1,18].

Table 2. Endpoints in study 1245.31 at 76 weeks[1,18].

	Empagliflozin 25 mg n = 224	Empagliflozin 10 mg n = 224
Adjusted mean % change from baseline in HbA1c (95% CI) vs. sitagliptin 100 mg	−0.22 (−0.38 to −0.07)	−0.12 (−0.28 to 0.04)
p vs. sitagliptin (HbA_{1c})	0.0050	0.1310
Adjusted mean change from baseline in body weight in kg (95% CI) vs. sitagliptin	−2.6 (−3.1 to −2.0)	−2.3 (−2.9 to −1.8)
p vs. sitagliptin (body weight)	< 0.001	< 0.001
Adjusted mean change from baseline in systolic blood pressure, mm Hg (95% CI) vs. sitagliptin	−3.8 (−6.0 to −1.6)	−3.7 (−5.9 to −1.6)
p vs. sitagliptin (systolic blood pressure)	< 0.001	< 0.001
Adjusted mean change from baseline in diastolic blood pressure, mm Hg (95% CI) vs. sitagliptin	−1.6 (−2.9 to −0.2)	−1.5 (-2.8 to −0.2)
p vs. sitagliptin (diastolic blood pressure)	< 0.05	< 0.05
CI: confidence interval; HbA_{1c} values can also be expressed in mmol/mol (see Glossary).		

3.3 Study 1275.1

Study 1275.1 was a randomised, double-blind, international, 24-week study with a two-week placebo run-in period in treatment naive T2DM patients who experienced insufficient glycaemic control[1,19]. Patients who successfully completed the run-in were randomised to enter the double-blind 52-week treatment period, after which patients entered a four-week follow-up. Patients did not receive any anti-diabetic therapy at least 12 weeks before pre-randomisation. Randomisation of patients (N = 677) was carried out in the ratio 1:1:1:1:1 into five study arms: empagliflozin 10 mg, empagliflozin 25 mg, linagliptin 5 mg, empagliflozin 25 mg/linagliptin 5 mg and empagliflozin 10 mg/linagliptin 5 mg. Study 1275.1 was designed to compare the effect of fixed dose combinations of empagliflozin/linagliptin versus the individual components and did not include statistical comparison of empagliflozin monotherapy versus linagliptin monotherapy. Patients entering the study were aged ≥ 18 years (mean age of 54.6 years) and had HbA_{1c} ≥ 7.0% and ≤ 10.5%. Individuals with impaired renal function, defined as eGFR < 60 mL/min were excluded from treatment. Results for the primary endpoint, the change from baseline in HbA_{1c} after 24 weeks of treatment and other endpoints are given in Table 3[1,19].

Table 3. Endpoints in study 1275.1[1,19].

	Empagliflozin 25 mg n = 133	Empagliflozin 10 mg n = 132	Linagliptin 5 mg n = 133
Primary endpoint			
Adjusted mean % change from baseline in HbA_{1c} (SE) at 24 weeks	−0.95 (0.07)	−0.83 (0.07)	−0.67 (0.07)
Other endpoints			
Adjusted mean change in body weight in kg at 24 weeks (SE)	−2.13 (0.36)	−2.27 (0.37)	−0.78 (0.36)
Adjusted mean % change from baseline in HbA_{1c} at 52 weeks (SE)	−1.01 (0.08)	−0.85 (0.08)	−0.51 (0.08)
Adjusted mean change in body weight in kg at 52 weeks (SE)	−2.72 (0.42)	−2.55 (0.44)	−0.16 (0.46)
SE: standard error; HbA_{1c} values can also be expressed in mmol/mol (see Glossary).			

3.4 Network meta-analysis

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3.5 Comparative safety

The most common adverse reactions reported in studies 1275.1 and 1245.20 were urinary tract infections (UTIs), headaches and hyperglycaemia[1]. The Committee for Medicinal Products for Human Use (CHMP) determined from a large group of studies that on average empagliflozin was not associated with an increased risk of UTIs but was associated with an increased risk of genital infections[8].

Empagliflozin was associated with a higher frequency of decreased renal function, genital infection and UTIs in patients with moderate renal impairment and is therefore not recommended in this group[8]. In addition, the efficacy of empagliflozin, as with other SGLT-2 inhibitors, is decreased in those with decreased renal function[8].

There was a higher frequency of UTIs, volume depletion and decreased renal function in patients aged ≥ 75 years and caution should be exercised in these patients[8].

CHMP reports that 19 patients who had received empagliflozin had serious liver enzyme elevation during or after treatment. In all but one case an independent committee of hepatic experts judged that the causal relationship with the treatment was not probable[8]. The Medicines and Healthcare products Regulatory Agency and European Medicines Agency have reported that the administration of SGLT-2 inhibitors has been linked to serious and potentially life-threatening cases of diabetic ketoacidosis (DKA)[20,21]. Clinicians are advised to test for raised ketone levels in patients with symptoms of DKA[20]. License holders have been requested to submit information related to cases of DKA and to address questions specifically related to this condition[21]. Although no effects on bone mineral density have been found during clinical trials, it is too early to assess the long term side effects of this medicine[8].

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3.6 AWTTC critique

- Empagliflozin is licensed for the treatment of T2DM in patients for whom metformin is inappropriate due to intolerance[2,3]. However no studies have been submitted in patients meeting this specific criterion. CHMP points out that such patients may be intolerant to metformin (gastrointestinal complaints) or have contraindications such as renal impairment (eGFR < 60 ml/min/1.73 m^2) or heart failure[8]. It is unlikely that gastrointestinal complaints due to metformin will influence the efficacy and safety of empagliflozin[8]. However, empagliflozin cannot be recommended in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) due to reduced efficacy in this group and the increased risk of adverse events and this is reflected in the SPCs[2,3,8]. Similarly patients with heart failure were not investigated in any of the studies[2,3,8]. Subsequent to these studies, EMPA-REG OUTCOME™, has been published[22]. This study specifically included patients with established cardiovascular disease and found that the addition of empagliflozin to current antidiabetic treatments (or as a first-line option) significantly reduced the risk of hospitalisation due to heart failure when compared to placebo (hospitalisation for heart failure was 2.7% in the empagliflozin group and 4.1% in the placebo group, hazard ratio 0.65, 95% confidence intervals: 0.50 to 0.85; p=0.002)[22]. Clinical experts contacted by AWTTC suggest that empagliflozin would be a treatment option in those patients intolerant of metformin who have preserved renal function (eGFR ≥ 60 ml/min/1.73 m^2) and who carry a significant cardiovascular risk as depicted in the EMPA-REG cohort of study patients[23].

- After 24 weeks empagliflozin monotherapy gave a similar HbA_{1c} reduction to sitagliptin compared to placebo. Empagliflozin treatment was associated with a decrease in body weight compared to sitagliptin[8]. These characteristics were maintained over a 76-week period as evidenced by the extension study. The benefit/risk profile of empagliflozin was consistent with that of other SGLT-2 inhibitors[8].
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4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] includes a cost-utility analysis (CUA) comparing the once daily oral antidiabetic drug empagliflozin 10 mg and 25 mg with once daily pioglitazone 45 mg, sitagliptin 100 mg, dapagliflozin 5 mg and 10 mg, and canagliflozin 100 mg and 300 mg; and all commonly prescribed sulfonylureas, which are considered as a class and tend to be administered in divided doses (i.e. no individual sulfonylurea drugs or doses have been included in the analysis). The submission also includes a cost-minimisation analysis comparing the once daily SGLT-2 inhibitors empagliflozin 10 mg and 25 mg, canagliflozin 100 mg and 300 mg, and dapagliflozin 5 mg and 10 mg.

The CUA takes the form of a two-part model, which adopts an NHS and social services perspective and a total time horizon of 41 years. The first year is modelled using a short-term decision tree, while the subsequent 40 years are modelled via long-term extrapolation of the United Kingdom Prospective Diabetes Study (UKPDS) OM1 outcomes model[24]. The Clinical Practice Research Datalink (CPRD) was used to extract data for 9,210 patients to inform the baseline characteristics of the economic model.

The short-term component of the CUA considers costs and utilities related to weight/body mass index (BMI), hypoglycaemic events and UTIs; these utilities are not incorporated in the long-term UKPDS OM1 model. The company has sought to populate the model with the longest duration of data possible; as a result, both 52 weeks and 24 weeks data were used.

The long term component of the model, the UKPDS OM1 simulation, produces discounted (3.5% per annum) estimates of life expectancy, quality adjusted life expectancy and costs of complications, together with 95% confidence intervals[24]. The main parameters affected by the treatments considered in this submission are HbA_{1c}, BMI/weight and systolic blood pressure.

Two phase III randomised controlled studies; study 1245.20[17] and study 1275.1[19], one long term 76-week extension study (study 1245.31)[18] and indirect treatment comparisons underpin the economic model. The phase III studies and extension study provide evidence of the efficacy and safety of empagliflozin, drawing comparisons with placebo, linagliptin and sitagliptin. NMA further informs the model in terms of the comparative clinical efficacy of other oral anti-diabetic drugs which were not directly compared with empagliflozin in the phase III studies.

The cost and utility data relevant to the economic analysis were sourced largely from a systematic review conducted for the empagliflozin combination therapy submission to NICE (TA336)[10] and a recently published, large-scale ten-year study focused on the costs of intermediate and long-term inpatient and non-inpatient costs associated with

T2DM related complications[25]. These data are supplemented, where necessary, with data from a number of other sources[26–31]; prescription costs are taken from MIMS[32].

The CUA model is characterised by a number of assumptions, including:

- No patients die within the first year of treatment
- No patients discontinue or switch treatment
- Costs and quality of life not related to treatment, or treatment-related adverse events, are not considered in year one
- Patients are only treated for one year, meaning that treatment efficacy is only experienced in the first year, before UKPDS OM1 is used for long-term extrapolation
- The costs of managing non-severe hypoglycaemia are assumed to be negligible
- The number of hypoglycaemic events is capped at one per year
- Severe and non-severe hypoglycaemia events are combined together
- Utility associated with weight loss only applies during the one year of treatment (where weight is reduced from baseline, it is considered to rebound immediately to baseline at 52 weeks)
- Some trials in the NMA do not report specific events which are included in the model. This led to the effects of sulfonylureas on UTIs and systolic blood pressure being assumed equal to placebo.

Probabilistic sensitivity analyses are conducted to test the robustness of the model and account for uncertainties of the following parameters:

- Baseline: BMI, height, annual risk of hypoglycaemia, annual risk of UTIs
- Utility associated with BMI, hypoglycaemia and UTIs
- Costs of hypoglycaemia and UTIs
- Relative risk of: hypoglycaemia, UTIs
- Weight gain/loss

Scenario analyses further explored the impact of two-way variation of all variables, the exclusion of all non-significant clinical differences, changes in baseline patient characteristics, and variation of the weight rebound period.

4.1.2 Results

The results of the base case analysis of the CUA are presented in Tables 4 and 5. Based on a modelled lifetime analysis, using 52-week efficacy data, once daily empagliflozin 10 mg and 25 mg are cost-effective treatment options at a willingness-to-pay (WTP) threshold of £20,000 per QALY compared to once daily administration of sitagliptin 100 mg and pioglitazone 45 mg, and divided doses of sulfonylurea. Both available dosages of empagliflozin dominate once daily administration of sitagliptin 100 mg (a DPP-4 inhibitor) when 52-week data are compared. However, when compared with SGLT-2 inhibitors using 24-week data, empagliflozin 10 mg and 25 mg given once daily dominate both dosages of dapagliflozin, but are dominated by once daily administration of canagliflozin 100 mg.

Table 4. Results of the base case analysis (52-week data)[1].

	Empagliflozin	Comparator	Difference
Empagliflozin 25 mg versus pioglitazone 45 mg			
Total costs	£22,598	£22,343	**£254**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 10 mg versus pioglitazone 45 mg			
Total costs	£22,622	£22,343	**£279**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 25 mg versus sitagliptin 100 mg			
Total costs	£22,598	£22,690	**-£93**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 10 mg versus sitagliptin 100 mg			
Total costs	£22,622	£22,690	**-£68**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 25 mg versus sulfonylureas			
Total costs	£22,598	£22,342	**£256**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 10 mg versus sulfonylureas			
Total costs	£22,622	£22,342	**£281**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 25mg versus empagliflozin 10mg			
Total costs	£22,598	£22,622	**-£25**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; ¶commercial in confidence data removed.

Table 5. Results of the base case analysis (24-week data)[1].

	Empagliflozin	Comparator treatment	Difference
Empagliflozin 25 mg versus canagliflozin 100 mg			
Total costs	£22,591	£22,561	**£30**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 10 mg versus canagliflozin 100 mg			
Total costs	£22,610	£22,561	**£50**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 25 mg versus canagliflozin 300 mg			
Total costs	£22,591	£22,620	**-£29**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 10 mg versus canagliflozin 300 mg			
Total costs	£22,610	£22,620	**-£10**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 25 mg versus dapagliflozin 5 mg			
Total costs	£22,591	£22,617	**-£26**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 10 mg versus dapagliflozin 5 mg			
Total costs	£22,610	£22,617	**-£6**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 25 mg versus dapagliflozin 10 mg			
Total costs	£22,591	£22,626	**-£35**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 10 mg versus dapagliflozin 10 mg			
Total costs	£22,610	£22,626	**-£15**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		
Empagliflozin 25 mg versus empagliflozin 10 mg			
Total costs	£22,591	£22,610	**-£20**
Total QALYs	¶	¶	¶
ICER (£/QALY gained)	¶		

ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year; ¶commercial in confidence data removed.

One-way sensitivity analyses were conducted to assess the impact of the variables incorporated in the short-term decision tree model on the incremental cost effectiveness ratio (ICER)s for the 24 week analysis. The results indicate that the ICER was most sensitive to the incidence of hypoglycaemic events (empagliflozin 25 mg and the comparator). Weight loss and the incidence of UTIs also have a considerable impact on the ICER. Other variables, including cost and utility decrements associated with AEs had a comparably minimal impact on the ICER results. Analysis of the comparisons versus empagliflozin 10 mg showed very similar results.

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In contrast, the cost-effectiveness acceptability curve generated via base case probabilistic analysis using 24-week data does not support empagliflozin being the most cost-effective treatment. This is because the ICERs are derived from analyses which reveal very small differences in costs and QALYs.

The majority of scenario analyses conducted resulted in no change to dominance findings and minimal changes to ICER values. The only two scenarios which resulted in a change in dominance are detailed in Table 6 below, along with the other scenarios which yielded the most notable results.

Table 6. Results of scenario analyses[1].

Scenarios	ICER	Plausibility
52-week treatment excluding non-statistically significant differences (comparisons vs. empagliflozin 25 mg)	¶	This scenario effectively removes the short term adverse events of hypoglycaemia and UTI's from the analyses. Given that empagliflozin tends to be associated with a slightly higher risk of hypoglycaemic events and UTIs compared to some of the other treatments analysed over the 52 week period, it is arguably more appropriate to consider the base case scenario.
24-week treatment excluding non-statistically significant differences (comparisons vs. empagliflozin 25 mg)	¶	This scenario effectively removes the short term adverse events of hypoglycaemia and UTI's from the analyses. Given that empagliflozin tends to be associated with a slightly higher risk of hypoglycaemic events compared to some of the other drugs analysed over a 24 week period, and has a wide confidence interval for this attribute, it is arguably more appropriate to consider the base case scenario.
24-week treatment excluding non-statistically significant differences (comparisons vs. empagliflozin 10 mg)	¶	No information is provided on the changes in parameter of this scenario. It is therefore not possible to assess its plausibility.
24 week treatment based on 52 week rebound period (comparisons vs. empagliflozin 10 mg)	¶	Given that the assumption of weight rebound is more reflective of model design requirements than of real-life observations, it is questionable whether this scenario offers any further benefit or insight over the base-case analyses.
¶commercial in confidence data removed		

The cost minimisation analysis, conducted solely on SGLT-2 inhibitors, concludes that it is likely that empagliflozin is as cost-effective as both once-daily doses of dapagliflozin (5 mg and 10 mg) and once-daily canagliflozin 100 mg, in view of the extremely small difference in QALYs and their equal acquisition costs. Given that empagliflozin has a lower pack price compared with canagliflozin 300 mg, the company suggests that empagliflozin would be expected to lead to cost savings for NHS Wales, assuming comparable QALYs between the two treatments.

4.1.3 AWTTC critique

While the results indicate that empagliflozin dominates some treatments and is dominated by others, absolute differences in both costs and benefits are very small, and similar cost-effectiveness may be assumed for most comparisons.

Strengths of the economic model:

- The submission provides a detailed, transparent account of methods, data sources and analyses undertaken. The company also acknowledges the main limitations of the evaluation and provides clear justifications for its choice of methods and assumptions. Extensive analyses are conducted to address

parameter uncertainties, including probabilistic sensitivity analyses of the UKPDS OM1 component of the model.

- The comparators included in the analysis appear appropriate; they are all licensed monotherapies for this patient group.
- The use of the CPRD database facilitated population of the model with representative patients.
- The time-frame of 41 years, somewhat dictated by the capacity of the UKPDS OM1 simulation model, would appear to be suitable given that: early control of diabetes can produce long-term benefits for patients; and the mean age of newly diagnosed patients in the CPRD dataset is ≥ 60 years[1].
- Whilst having the potential to oversimplify the economic analysis, including the treatment of patients in the first year only avoids having to make longer term assumptions.
- The UKPDS OM1 simulation model used for extrapolation is a validated, robust model.

Limitations of the economic model:

- The model assumes that patients are treated for one year only. The UKPDS OM1 model does not include any treatment effect or cost after the first year or treatment changes. This limits the usefulness of the model, although no data were provided to support the use of empagliflozin for longer than 52 weeks
- The use of indirect treatment comparisons has the potential to introduce bias.
- Indirect treatment comparisons have necessitated the use of both 24- and 52-week data to populate the model; this also introduces some bias.
- The model includes sulfonylureas as a class of treatment, rather than analysing each individual medicine within this group. This limits pragmatic comparisons on a medicine versus medicine basis.
- The studies used to establish efficacy of empagliflozin[17–19] do not include patients from the UK. The majority of studies included in the NMA are also not UK focused. This potentially has implications for generalisability to the Welsh setting.
- The baseline characteristics extracted from the CPRD dataset are UK specific rather than Wales specific. The company has attempted to address this via sensitivity analysis; however, the company suggests that this has resulted in the modelled population being more representative of the Welsh population in general, not the Welsh population with T2DM.
- Given that the choice of short-term adverse events is limited to three measures; it remains unknown whether inclusion of others would alter the ICERs.
- The capping of hypoglycaemic events to one per year and the exclusion of weight disutility measures in the model introduces some bias. However, the company states that given that empagliflozin is generally associated with weight loss and that once daily empagliflozin 25 mg tends to be associated with a lower risk of hypoglycaemic events, the bias is unlikely to be in the favour of empagliflozin.
- The CMA is not based on studies of therapeutic equivalence and may therefore not be appropriate. Neither canagliflozin nor dapagliflozin, despite being licensed as monotherapies, are currently recommended in the UK for this indication.
- Treatment discontinuation is not included in the short-term decision tree as the company states that no data was available. The company argues that data was taken from intention-to-treat analyses and discontinuation would therefore be reflected in the outcomes.
- The serious adverse event of DKA has not been specifically built into the model or mentioned as being particularly pertinent in the economic submission.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The prevalence of diabetes in Wales for the period 2015 to 2019 is estimated using population statistics and projections from Stats Wales[33] combined with a prevalence rate of 6.7% for Wales, as reported by Diabetes UK in 2013[6]. Approximately 90% of diabetic patients are diagnosed with T2DM[6]. Applying this proportion, the company estimates the total number of patients in Wales with T2DM over the five years. Using prescribing data for all T2DM[1] the company approximates that 53% of this patient group are prescribed monotherapy, and identifies the number of patients prescribed each available type of monotherapy. Empagliflozin is expected to be prescribed to 5% of patients in this group. The implications of this change in treatment are modelled by comparing the current prescribing patterns and associated costs, with those of a future treatment pathway that additionally recommends empagliflozin as a monotherapy. Sensitivity analyses explore how the budget model responds to changes in the uptake rate of SGLT-2 inhibitors, from 5% to 2% and 7%.

The budget impact analysis is guided by a number of key assumptions, including:

- The proportion of patients treated with SGLT-2 inhibitor monotherapy will increase from 1% to 5% with the introduction of empagliflozin.
- The prevalence and the uptake rate will remain constant at 6.7% and 5% respectively, over the five years.
- The proportion of patients treated with sulfonylurea will decrease from 63% to 61% with the introduction of empagliflozin.
- The proportion of patients treated with thiazolidinedione will decrease from 3% to 1% with the introduction of empagliflozin.

5.1.2 Results

The budget impact analyses reveal increased costs associated with drug acquisition for this patient group generated by the introduction of empagliflozin as a monotherapy. Table 7 details the projected net and cumulative cost implications for Wales in the five years following introduction. Table 8 provides a summary of the results of the sensitivity analyses.

Table 7. Company-reported costs associated with use of empagliflozin as monotherapy treatment for patients with T2DM unable to tolerate metformin[1].

	Year 1 (2015)	Year 2 (2016)	Year 3 (2017)	Year 4 (2018)	Year 5 (2019)
Number of eligible patients	99,302	99,694	100,092	100,487	100,883
Uptake (%)	5%	5%	5%	5%	5%
Number of patients treated with empagliflozin	4,965	4,985	5,005	5,024	5,044
Total cost without empagliflozin monotherapy	£17,595,815	£17,665,217	£17,735,746	£17,805,899	£17,875,958
Total cost with empagliflozin monotherapy	£19,230,624	£19,306,474	£19,383,556	£19,460,227	£19,536,796
Overall net cost	**£1,634,809**	**£1,641,257**	**£1,647,810**	**£1,654,328**	**£1,660,838**

Table 8. Results of the sensitivity analyses – varying the uptake of empagliflozin[1].

Treatment	Year 1 (2015)	Year 2 (2016)	Year 3 (2017)	Year 4 (2018)	Year 5 (2019)
Assumed uptake rate of empagliflozin monotherapy is 2%					
Net budget impact if market share of SGLT-2 inhibitors is 2%	£428,661	£430,352	£432,070	£433,779	£435,486
Assumed uptake rate of empagliflozin monotherapy is 7%					
Net budget impact if market share of SGLT-2 inhibitors is 7%	£2,373,588	£2,382,950	£2,392,464	£2,401,927	£2,411,378

5.1.3 AWTTC critique

- The submission gives a detailed and transparent account of the methods and data sources used in the budget impact analysis.
- The impact analysis is relatively comprehensive in including sulfonylureas, DDP-4 inhibitors, pioglitazone and SGLT-2 inhibitors, although a number of smaller market share comparators have been omitted.
- The uptake and prevalence rates are assumed to remain constant and no mortality rate is incorporated into the model. The market shares have been calculated using company internal patient data and thus the probability of the budget forecast being realistic is unclear.
- The sensitivity analyses explore the likely impact of changes in the predicted uptake rate for empagliflozin. However, details are not specifically provided in relation to how these changes are presumed to influence the market shares of comparators, which would have enhanced transparency.
- The budget impact analysis includes drug acquisition costs only. It does not include treatment effect related costs or potential longer term resource savings.

5.2 Comparative unit costs

Annual and 28 day acquisition costs for antidiabetic monotherapies are detailed in Table 9. Where the costs presented below take the form of ranges, these represent the minimum and maximum costs associated with drug acquisition. In some cases mid-level doses are more costly than higher ones, thus the ranges do not necessarily reflect the costs for minimum and maximum dosage. The drugs included represent

treatments listed in the British National Formulary as monotherapy options for the patient population covered by this submission[34]. The costs of canagliflozin and dapagliflozin have been included for completeness.

Table 9. Examples of medicine acquisition costs for oral antidiabetic monotherapies for patients with T2DM.

Regimens	Frequency	Approximate annual cost per patient
SGLT-2 Inhibitors		
Empagliflozin (Jardiance®▼)	10 mg–25 mg once daily	£477
Canagliflozin (Invokana®▼)	100 mg–300 mg once daily	£477
Dapagliflozin (Forxiga®▼)	5 mg (if hepatic impairment) or 10 mg once daily	£477
Sulfonylureas		
Glibenclamide (non-prop)	Initially 5 mg once daily – adjust according to response up to a maximum of 15 mg daily	£14–£43
Gliclazide (non-prop)	Initially 40-80 mg daily – adjust according to response up to a maximum of 320 mg daily	£10–£39
Gliclazide Modified Release (non-prop)	Initially 30 mg daily – adjust according to response up to a maximum of 120 mg daily	£27–£107
Glimepiride (non-prop)	Initially 1 mg daily – adjust according to response up to a maximum of 4 mg, or 6 mg in exceptional circumstances	£14–£111
Glipizide (Minodiab®)	Initially 2.5–5 mg once daily – adjust according to response up to a maximum of 20 mg daily (given in divided doses) orally	£8–£66
Tolbutamide (non-prop)	0.5–1.5 g (up to a maximum of 2 g) once daily or in divided doses	£267–£1069
Alpha Glucosidases Inhibitors		
Acarbose (Glucobay®)	Initially 50 mg daily, increased to 50 mg TDS, then increased 100 mg TDS, to a max of 200 mg TDS daily if necessary (minimum dosing assumption of 50 mg TDS for costing purposes)	£89–£329
Thiazolidinediones		
Pioglitazone (non prop)	Initially 15-30 mg once daily, increased to 45 mg once daily according to response	£16–£22
Repaglinide (non prop)	Initially 500 microgram TDS, up to a maximum 16 mg (4 mg QDS) according to response	£106–£191
DPP-4 inhibitors		
Linagliptin (Trajenta®▼)	5 mg once daily	£434
Saxagliptin (Onglyza®)	2.5 mg (if mod-severe renal impairment) or 5 mg once daily	£412
Sitagliptin (Januvia®)	25–50 mg (if severe-mod renal impairment, respectively) or 100 mg once daily	£434
Vildagliptin (Galvus®)	50 mg once daily (if mod-severe renal impairment) or 50 mg BD	£207–£414

See relevant Summaries of Product Characteristics for full licensed indications and dosing details[2,3,35–49].
Costs are based on British National Formulary prices as of September 2015[34].
Costs of monitoring are not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.
BD: twice daily; TDS: three times daily; QDS: four times daily

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, empagliflozin (Jardiance®▼) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

The company do not anticipate that empagliflozin (Jardiance®▼) will be supplied by a home healthcare provider[1].

6.2 Ongoing studies

The company submission highlighted EMPA-REG OUTCOME™, a study to investigate the safety of empagliflozin in patients with T2DM and with high cardiovascular risk[50]. Patients (N = 7,020) in the study were randomised (1:1:1) to receive either empagliflozin 10 mg, empagliflozin 25 mg or placebo in addition to their current antidiabetic medicines (only 2% of patients were treatment-naive prior to entering the study). This study completed in April 2015 and results were published at the time of writing this report. The primary composite outcome, death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke occurred in 490/4687 (10.5%) of patients in the pooled empagliflozin group and in 282/2333 (12.1%) of those in the placebo arm (hazard ratio in the empagliflozin group, 0.86; 95% confidence interval, 0.74 to 0.99; p = 0.04 for superiority). The median observation time was 3.1 years. Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events[22].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 28 July 2015.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Glycosylated haemoglobin (HbA_{1c})

This reflects the blood glucose level of a patient, where a higher HbA_{1c} level means more glucose has been present in the blood in the preceding few months. HbA_{1c} results are reported as a percentage; however, laboratories in the UK have switched to reporting results as mmol/mol[51,52] (see Table 10).

Table 10. Comparison of HbA_{1c} units[51].

HbA_{1c} (%)	HbA_{1c} (mmol/mol)
6.0	42
6.5	48
7.0	53
7.5	58
8.0	64
9.0	75

REFERENCES

1 Boehringer Ingelheim Ltd. Form B: Detailed appraisal submission. Empagliflozin (Jardiance®▼). 2015.

2 Boehringer Ingelheim Ltd. Jardiance®▼. Summary of Product Characteristics. 10 mg film-coated tablets. Jan 2015. Available at: https://www.medicines.org.uk/emc/medicine/28973. Accessed Jul 2015.

3 Boehringer Ingelheim Ltd. Jardiance®▼. Summary of Product Characteristics. 25 mg film-coated tablets. Jan 2015. Available at: https://www.medicines.org.uk/emc/medicine/28974. Accessed Jul 2015.

4 National Institute for Health and Care Excellence. Clinical Guideline 87. Type 2 diabetes. The management of type 2 diabetes. 2009. Available at: http://guidance.nice.org.uk/CG87. Accessed Jul 2015.

5 Welsh Government. National service framework for diabetes. Sep 2010. Available at: http://gov.wales/topics/health/publications/health/guidance/diabetes/?lang=en. Accessed Jul 2015.

6 Diabetes UK. Diabetes: Facts and Stats. 2014. Available at: https://www.diabetes.org.uk/Documents/About%20Us/Statistics/Diabetes-key-stats-guidelines-April2014.pdf. Accessed Sep 2015.

7 National Institute for Health and Care Excellence. Pathway for Managing type 2 diabetes. 2015. Available at: http://pathways.nice.org.uk/pathways/diabetes#path=view%3A/pathways/diabetes/managing-type-2-diabetes.xml&content=view-index. Accessed Jul 2015.

8 European Medicines Agency. Assessment Report for Jardiance. Procedure No.: EMEA/CHMP/137741/2014. Mar 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002677/WC500168594.pdf. Accessed Jul 2015.

9 National Institute for Health and Care Excellence. Diabetes (type 2) - canagliflozin, dapagliflozin and empagliflozin (monotherapy) [ID756]. Anticipated publication May 2016. Aug 2015. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-tag471. Accessed Aug 2015.

10 National Institute for Health and Care Excellence. Technology Appraisal TA336. Empagliflozin in combination therapy for treating type 2 diabetes. 2015. Available at: http://guidance.nice.org.uk/TA336. Accessed Jul 2015.

11 Scottish Intercollegiate Guidelines Network. Management of diabetes. A national clinical guideline. Mar 2010. Available at: http://www.sign.ac.uk/pdf/sign116.pdf. Accessed Aug 2015.

12 All Wales Medicines Strategy Group. linagliptin (Trajenta) 5 mg film-coated tablet. Reference No. 1667. Appraisal information. 2013. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1667. Accessed Jul 2015.

13 All Wales Medicines Strategy Group. vildagliptin (Galvus®) 50 mg tablet. Reference No. 1531. Appraisal information. Mar 2013. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1531. Accessed Jul 2015.

14 All Wales Medicines Strategy Group. sitagliptin (Januvia®) 25 mg and 50 mg film-coated tablet. Reference No. 1655. Appraisal information. Oct 2012. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1655. Accessed Jul 2015.

15 All Wales Medicines Strategy Group. AWMSG advice. Dapagliflozin (Forxgia®) . Reference number: 2745. Jun 2015. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/2745. Accessed Aug 2015.

16 All Wales Medicines Strategy Group. AWMSG advice. Canagliflozin (Invokana®) . Reference number: 2747. Jul 2015. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/2747. Accessed Aug 2015.
17 Roden M, Weng J, Eilbracht J et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised , double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes and Endocrinology* 2013; 1 (3): 208-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24622369. Accessed: Aug 2015.
18 Roden M, Weng J, Merker L et al. Empagliflozin (EMPA) monotherapy for > 76 weeks in drug naive patients with type 2 diabetes (T2DM). Presented at 74th Scientific Session of the American Diabetes Association. 13 Jun 2014.
19 Lewin A, DeFronzo RA, Patel S et al. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. *Diabetes Care* 2015; 38: 394-402. Available at: http://care.diabetesjournals.org/content/38/3/394.short. Accessed: Aug 2015.
20 Medicines and Healthcare products Regulatory Agency. SGLT 2 inhibitors (canagliflozin, dapagliflozin, empagliflozin): risk of diabetic ketoacidosis. Jun 2015. Available at: https://www.gov.uk/drug-safety-update/sglt2-inhibitors-canagliflozin-dapagliflozin-empagliflozin-risk-of-diabetic-ketoacidosis. Accessed Sep 2015.
21 European Medicines Agency. PRAC list of questions (to be addressed by the marketing authorisation holders). Jun 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors__20/Procedure_started/WC500187927.pdf. Accessed Sep 2015.
22 Zinman B, Wanner C, Lachin JM et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *NEJM* 2015; Epub ahead of print. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26378978. Accessed: Sep 2015.
23 All Wales Medicines Strategy Group. Empagliflozin (Jardiance®▼) 2746 Clinical Expert summary. 2015. Accessed Oct 2015.
24 Clarke PM, Gray AM, Briggs A et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). *Diabetologia* 2004; 47 (10): 1747-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Clarke+PM%2C+Gray+AM%2C+Briggs+A%2C+Farmer+AJ%2C+Fenn+P%2C+Stevens+RJ%2C+et+al.+A+model+to+estimate+the+lifetime+health+outcomes+of+patients+with+type+2+diabetes%3A+the+United+Kingdom+Prospective+Diabetes+Study+(UKPDS)+Outcomes+Model+(UKPDS+no.+68).+Diabetologia.+2004%3B47(10)%3A1747-59. Accessed: Sep 2015.
25 Alva ML, Gray A, Mihaylova B et al. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). *Diabetic medicine* 2015; 32 (4): 459-66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Alva+Gray+UKPDS. Accessed: Sep 2015.
26 National Institute for Health and Care Excellence. Appendix F: Full Health Economics Report. 2015. Available at: https://www.nice.org.uk/guidance/gid-cgwave0612/documents/type-2-diabetes-appendix-f2. Accessed Sep 2015.
27 National Institute for Health and Care Excellence. Technology Appraisal TA288. Dapagliflozin in combination therapy for treating type 2 diabetes. 2015. Available at: http://guidance.nice.org.uk/TA288. Accessed Sep 2015.
28 Burslem K, Das Gupta R, Hussein A. Estimating the average annual cost of treatment with insulin for patients with type 2 diabetes mellitus. *Value in Health* 2011; 14 (7): A478. Available at:

http://www.valueinhealthjournal.com/article/S1098-3015(11)02901-9/abstract. Accessed: Sep 2015.
29 Currie CJ, Morgan CL, Poole CD et al. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. *Curr Med Res Opin* 2006; 22 (8): 1523-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Multivariate+models+of+health-related+utility+and+the+fear+of+hypoglycaemia+in+people+with+diabetes. Accessed: Sep 2015.
30 Barry HC, Ebell MH, Hickner J. Evaluation of suspected urinary tract infection in ambulatory women: a cost-utility analysis of office-based strategies. *The Journal of Family Practice* 1997; 44 (1): 49-60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9010371. Accessed: Sep 2015.
31 Bagust A, Beale S. Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. *Health Economics* 2005; 14 (3): 217-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Modelling+EuroQol+CODE+Bagust . Accessed: Sep 2015.
32 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2015. Available at: http://www.mims.co.uk/.
33 Welsh Government. Stats Wales: population projections by year and gender. 2012. Available at: https://statswales.wales.gov.uk/Catalogue/Population-and-Migration/Population/Projections/National/2012-Based/PopulationProjections-by-Year-Gender. Accessed Sep 2015.
34 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. 2015. Available at: https://www.medicinescomplete.com/mc/bnf/current/. Accessed Sep 2015.
35 AstraZeneca UK limited. Forxiga®▼. Summary of Product Characteristics. 5 mg and 10 mg film-coated tablets. Oct 2014. Available at: https://www.medicines.org.uk/emc/medicine/27188. Accessed Sep 2015.
36 AstraZeneca UK limited. Onglyza®. Summary of Product Characteristics. 2.5 mg and 5 mg film-coated tablets. May 2015. Available at: https://www.medicines.org.uk/emc/medicine/22315. Accessed Sep 2015.
37 Boehringer Ingelheim Ltd. Trajenta®▼. Summary of Product Characteristics. 5 mg film-coated tablets. Oct 2014. Available at: https://www.medicines.org.uk/emc/medicine/25000. Accessed Sep 2015.
38 Janssen-Cilag Ltd. Invokana®▼. Summary of Product Characteristics. 100 mg film-coated tablets. Aug 2015. Available at: https://www.medicines.org.uk/emc/medicine/28400. Accessed Sep 2015.
39 Merck Sharp and Dohme Ltd. Januvia®. Summary of Product Characteristics. 100 mg film-coated tablets. Aug 2015. Available at: https://www.medicines.org.uk/emc/medicine/19609. Accessed Sep 2015.
40 Novartis Pharmaceuticals UK Ltd. Galvus®. Summary of Product Characteristics. 50 mg film-coated tablets. Jun 2015. Available at: https://www.medicines.org.uk/emc/medicine/20734. Accessed Sep 2015.
41 Winthrop Pharmaceuticals UK limited. Zentiva®. Summary of Product Characteristics. 15 mg film-coated tablets. Dec 2014. Available at: https://www.medicines.org.uk/emc/medicine/25674. Accessed Sep 2015.
42 Wockhardt UK limited. Glibenclamide. Summary of Product Characteristics. 5 mg tablets. Jun 2015. Available at: https://www.medicines.org.uk/emc/medicine/30410. Accessed Sep 2015.
43 Wockhardt UK limited. Gliclazide. Summary of Product Characteristics. 80 mg tablets. Jun 2013. Available at: https://www.medicines.org.uk/emc/medicine/27762. Accessed Sep 2015.
44 Consilient Health Limited. Laaglyda® MR. Summary of Product Characteristics. 60 mg modified-release tablets. Nov 2013. Available at: https://www.medicines.org.uk/emc/medicine/28358. Accessed Sep 2015.

45 Accord Healthcare Limited. Glimepiride. Summary of Product Characteristics. 1 mg tablets. Sep 2014. Available at: https://www.medicines.org.uk/emc/medicine/25813. Accessed Sep 2015.
46 AstraZeneca UK limited. Minodiab®. Summary of Product Characteristics. 5 mg tablets. Aug 2014. Available at: https://www.medicines.org.uk/emc/medicine/9851. Accessed Sep 2015.
47 Kent Pharmaceuticals Limited. Tolbutamide. Summary of Product Characteristics. 500 mg tablets. Jan 2013. Available at: https://www.medicines.org.uk/emc/medicine/26366. Accessed Sep 2015.
48 Bayer plc. Glucobay®. Summary of Product Characteristics. 100 mg tablets. Sep 2015. Available at: https://www.medicines.org.uk/emc/medicine/19973. Accessed Sep 2015.
49 Actavis UK Ltd. Repaglinide. Summary of Product Characteristics. 0.5 mg tablets. Jan 2014. Available at: https://www.medicines.org.uk/emc/medicine/24635. Accessed Sep 2015.
50 Boehringer Ingelheim Ltd. NCT01131676 Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients (EMPA-REG-OUTCOME). May 2015. Available at: https://clinicaltrials.gov/ct2/show/study/NCT01131676?term=EMPA-REG+OUTCOME&rank=1. Accessed Aug 2015.
51 Diabetes UK. Testing. 2015. Available at: https://www.diabetes.org.uk/Guide-to-diabetes/Monitoring/Testing/. Accessed Sep 2015.
52 Diabetes UK. HbA1c reporting methods set to change. Sep 2011. Available at: https://www.diabetes.org.uk/About_us/News_Landing_Page/HbA1c-reporting-methods-set-to-change/. Accessed Sep 2015.