NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Empagliflozin in combination therapy for treating type 2 diabetes

Appendices

Appendix A: The diagrams and results of the network meta-analyses

Figure 1 Network of trials for dual therapy (in combination with metformin)

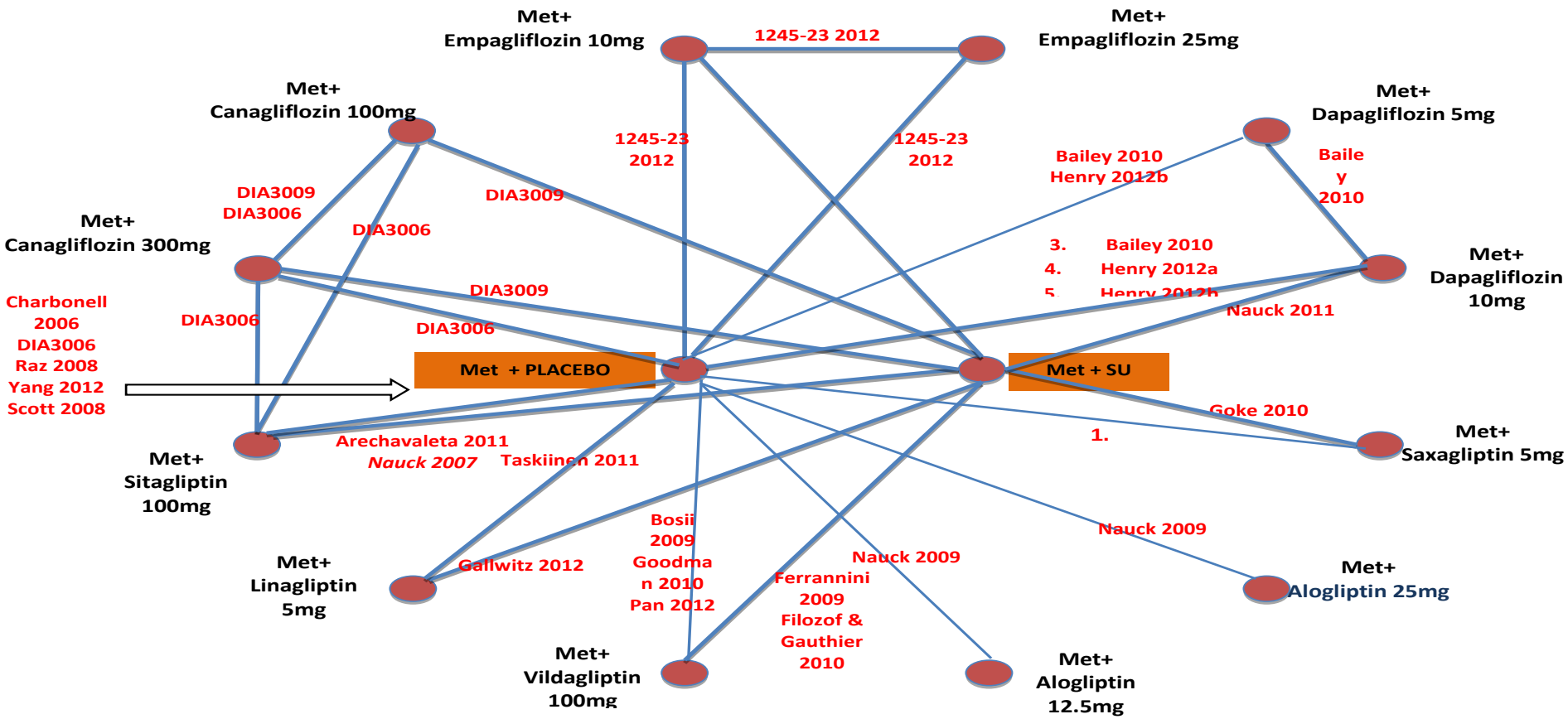

Figure 2 Network of trials for triple therapy (in combination with metformin plus a sulfonylurea)

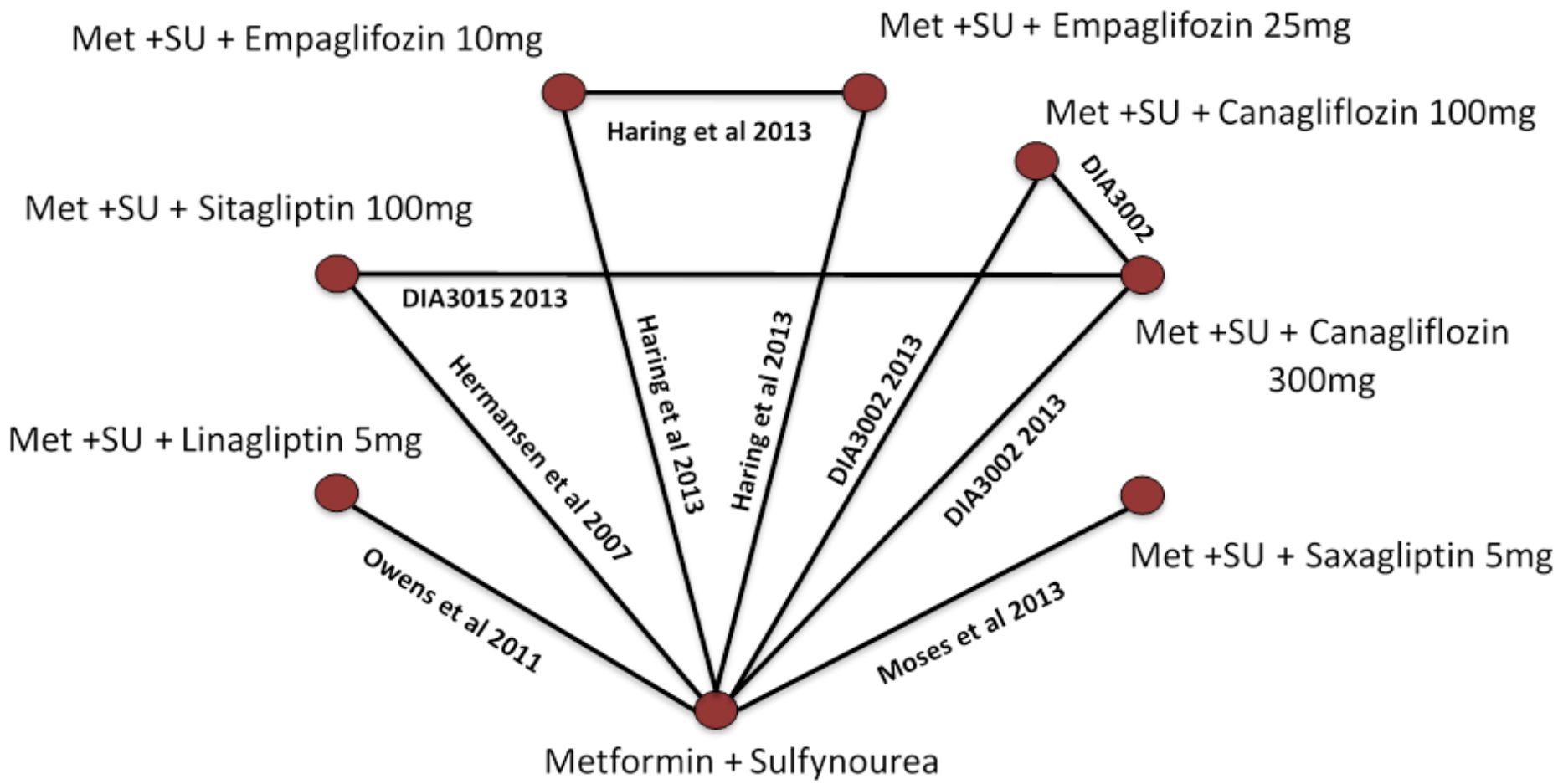

Figure 3 Network of trials for add-on to insulin therapies

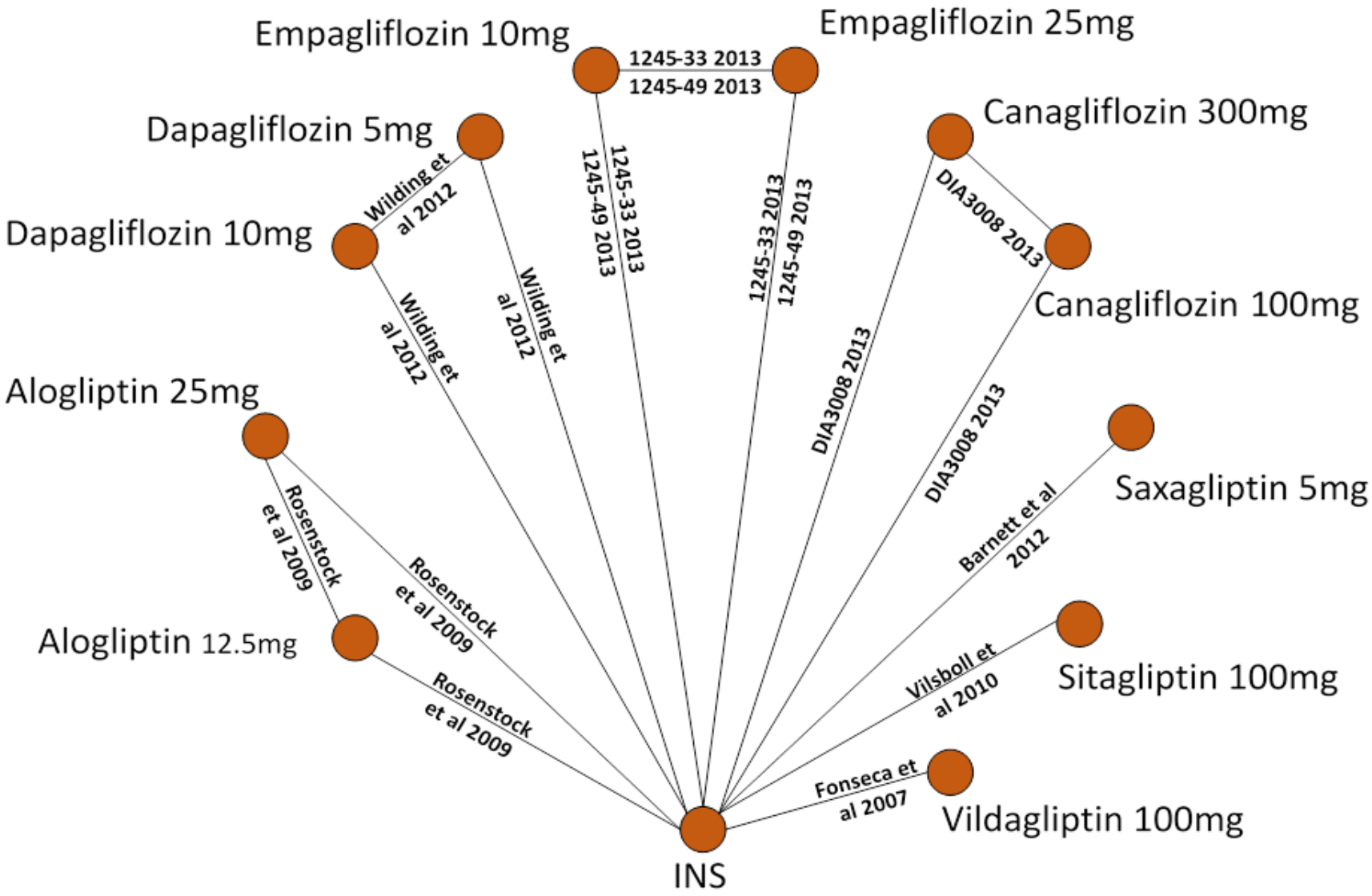

Figure 4 Network of trials for dual therapy (in combination with thiazolidinedione)

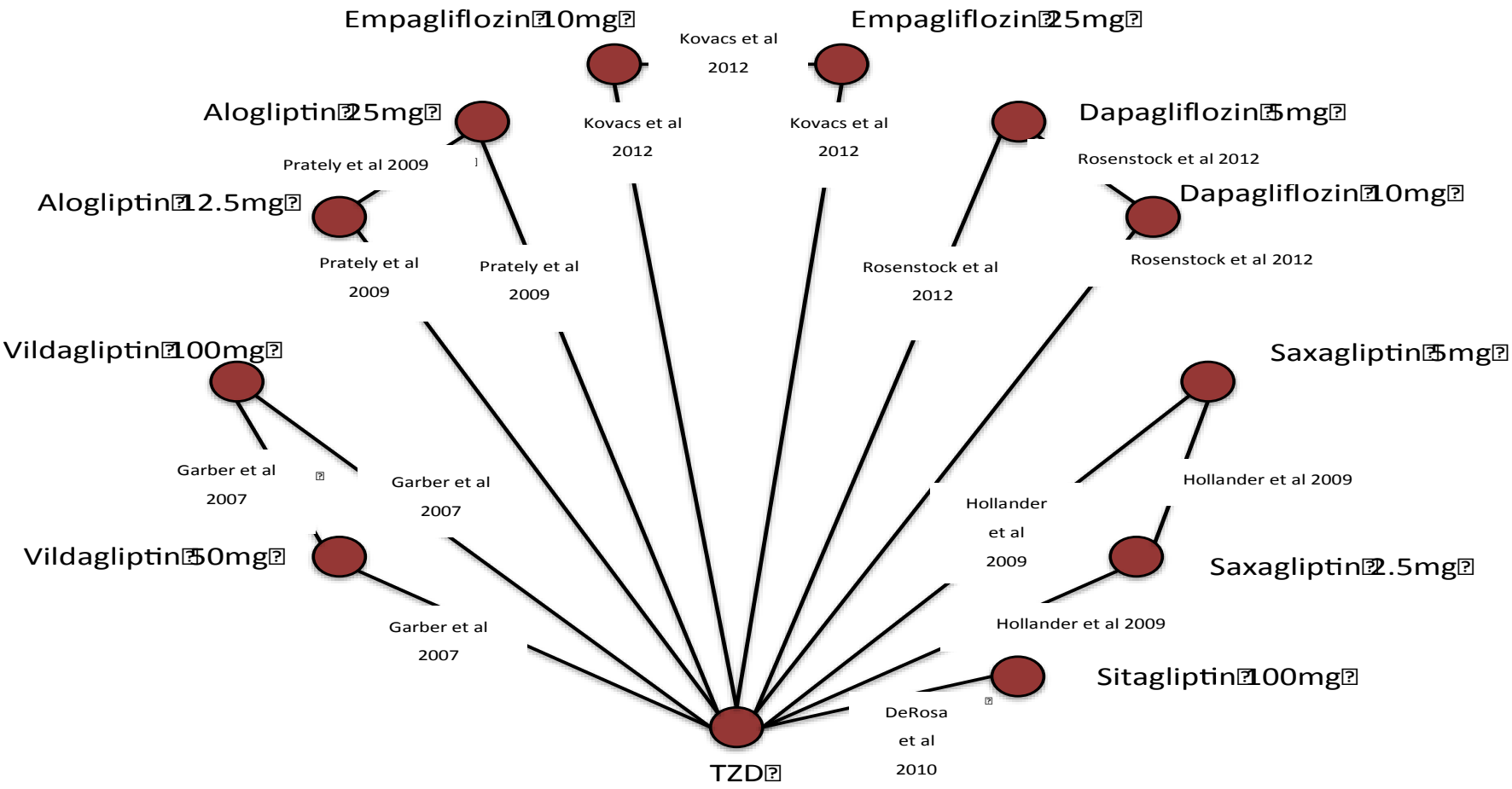

Figure 5 Network of trials for triple therapy (in combination with metformin plus a thiazolidinedione)

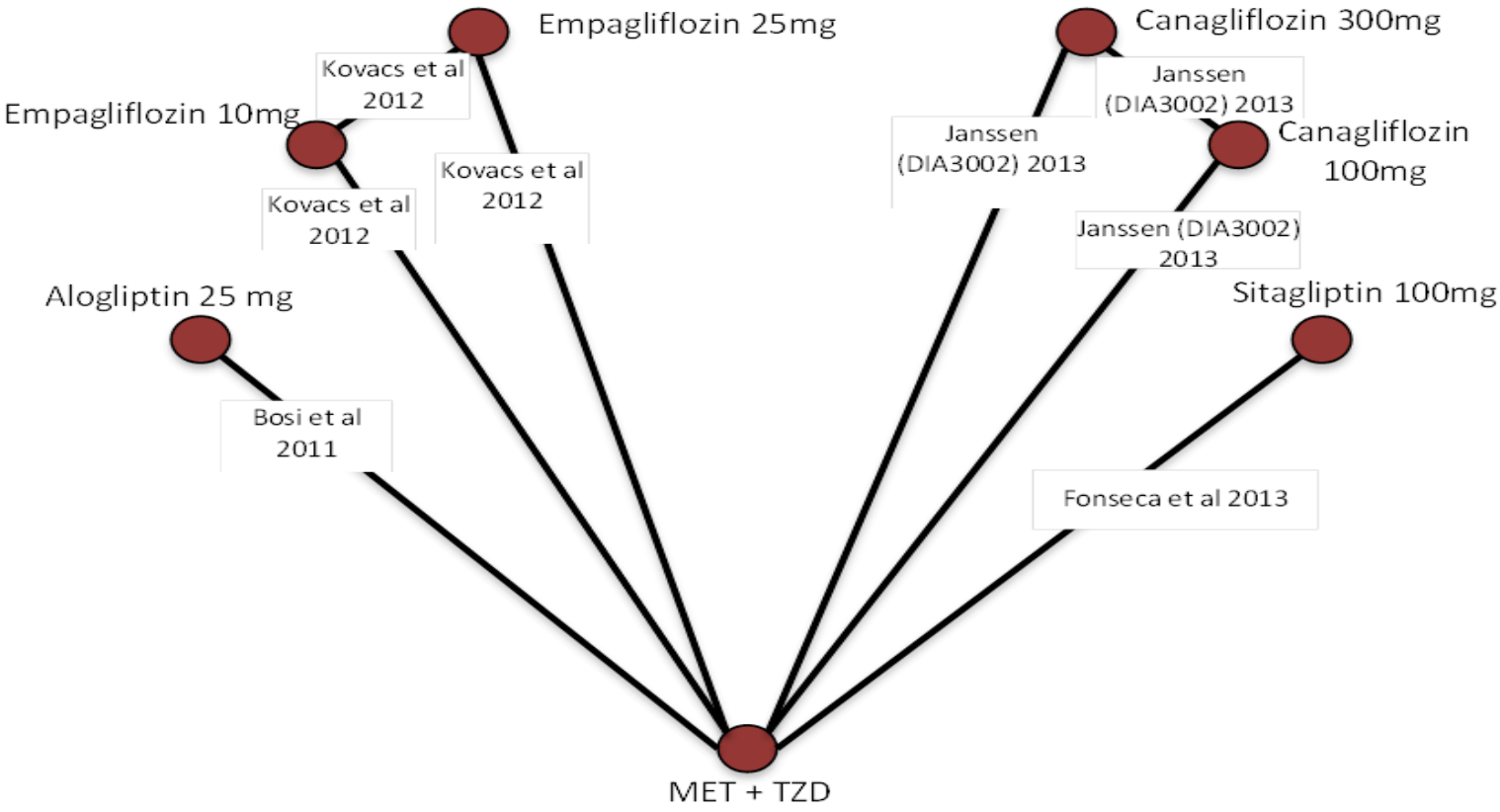

Figure 6 Summary of NMA results for mean change (%) in HbA1c at 24 ± 4 weeks (values less than 0 indicates empagliflozin superior)

	empag	comparator	MD	LCI	UCI
Dual	empag 25	empag 10	-0.1	-0.44	0.23
Dual	empag 25	Canagliflozin 100mg	-0.03	-0.39	0.32
Dual	empag 25	Canagliflozin 300mg	0.09	-0.26	0.44
Dual	empag 25	Dapagliflozin 5mg	-0.23	-0.6	0.15
Dual	empag 25	Dapagliflozin 10mg	-0.14	-0.46	0.17
Dual	empag 25	Sitagliptin 100mg	0.09	-0.2	0.39
Dual	empag 10	empag 25	0.1	-0.23	0.44
Dual	empag 10	Canagliflozin 100mg	0.07	-0.35	0.49
Dual	empag 10	Canagliflozin 300mg	0.19	-0.22	0.61
Dual	empag 10	Dapagliflozin 5mg	-0.13	-0.56	0.31
Dual	empag 10	Dapagliflozin 10mg	-0.04	-0.42	0.34
Dual	empag 10	Sitagliptin 100mg	0.19	-0.17	0.57
Triple	empag 25	empag 10	0.05	-0.09	0.19
Triple	empag 25	Canagliflozin 100mg	0.16	-0.09	0.41
Triple	empag 25	Canagliflozin 300mg	0.41	0.2	0.63
Triple	empag 25	Dapagliflozin 5mg	ND	ND	ND
Triple	empag 25	Dapagliflozin 10mg	ND	ND	ND
Triple	empag 25	Sitagliptin 100mg	0.21	-0.01	0.43
Triple	empag 10	empag 25	-0.05	-0.19	0.09
Triple	empag 10	Canagliflozin 100mg	0.11	-0.13	0.36
Triple	empag 10	Canagliflozin 300mg	0.36	0.15	0.58
Triple	empag 10	Dapagliflozin 5mg	ND	ND	ND
Triple	empag 10	Dapagliflozin 10mg	ND	ND	ND
Triple	empag 10	Sitagliptin 100mg	0.16	-0.05	0.38
insulin + on	empag 25	empag 10	-0.07	-0.19	0.04
insulin + on	empag 25	Canagliflozin 100mg	0.07	-0.14	0.27
insulin + on	empag 25	Canagliflozin 300mg	0.16	-0.05	0.36
insulin + on	empag 25	Dapagliflozin 5mg	-0.07	-0.27	0.12
insulin + on	empag 25	Dapagliflozin 10mg	0.00	-0.19	0.19
insulin + on	empag 25	Sitagliptin 100mg	0.03	-0.2	0.25
insulin + on	empag 10	empag 25	0.07	-0.04	0.19
insulin + on	empag 10	Canagliflozin 100mg	0.14	-0.06	0.34
insulin + on	empag 10	Canagliflozin 300mg	0.23	0.03	0.43
insulin + on	empag 10	Dapagliflozin 5mg	0	-0.19	0.19
insulin + on	empag 10	Dapagliflozin 10mg	0.07	-0.12	0.26
insulin + on	empag 10	Sitagliptin 100mg	0.1	-0.12	0.32

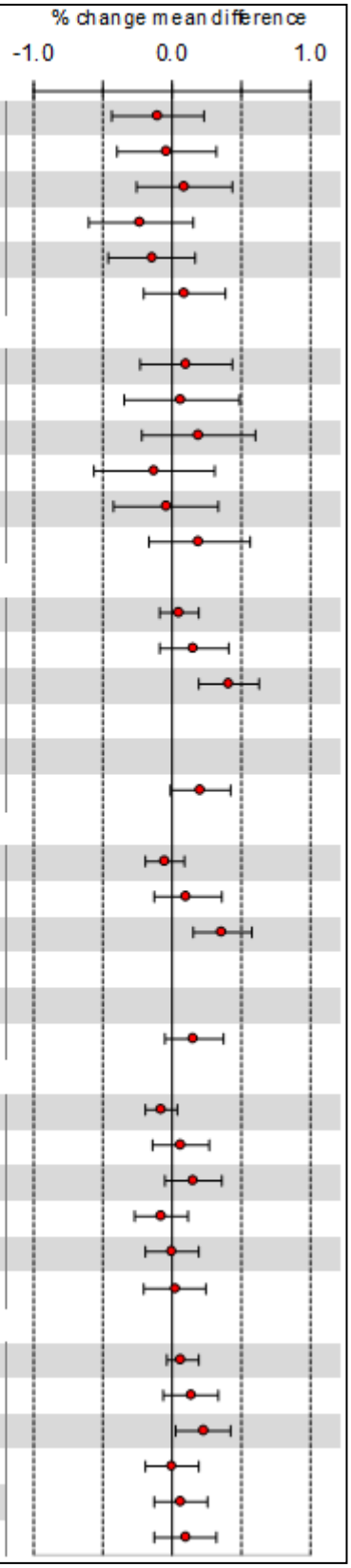

Figure 7 Summary of NMA results for mean change (kg) in body weight at 24 ± 4 weeks (values less than 0 indicates empagliflozin superior)

	empag	comparator	MD	LCI	UCI
Dual	empag 25	empag 10	-0.44	-1.02	0.13
Dual	empag 25	Canagliflozin 100mg	0.18	-0.49	0.93
Dual	empag 25	Canagliflozin 300mg	0.9	0.2	1.64
Dual	empag 25	Dapagliflozin 5mg	0.07	-0.65	0.83
Dual	empag 25	Dapagliflozin 10mg	0.24	-0.4	0.91
Dual	empag 25	Sitagliptin 100mg	-2.22	-2.85	-1.49
Dual	empag 10	empag 25	0.44	-0.13	1.02
Dual	empag 10	Canagliflozin 100mg	-0.24	-0.79	0.35
Dual	empag 10	Canagliflozin 300mg	0.45	-0.1	1.05
Dual	empag 10	Dapagliflozin 5mg	-0.37	-0.97	0.29
Dual	empag 10	Dapagliflozin 10mg	-0.2	-0.68	0.33
Dual	empag 10	Sitagliptin 100mg	-2.65	-3.12	-2.09
Triple	empag 25	empag 10	-0.23	-0.66	0.2
Triple	empag 25	Canagliflozin 100mg	-0.74	-1.51	0.03
Triple	empag 25	Canagliflozin 300mg	-0.31	-0.99	0.39
Triple	empag 25	Dapagliflozin 5mg	ND	ND	ND
Triple	empag 25	Dapagliflozin 10mg	ND	ND	ND
Triple	empag 25	Sitagliptin 100mg	-2.97	-3.67	-2.27
Triple	empag 10	empag 25	0.23	-0.2	0.66
Triple	empag 10	Canagliflozin 100mg	-0.51	-1.26	0.24
Triple	empag 10	Canagliflozin 300mg	-0.07	-0.75	0.6
Triple	empag 10	Dapagliflozin 5mg	ND	ND	ND
Triple	empag 10	Dapagliflozin 10mg	ND	ND	ND
Triple	empag 10	Sitagliptin 100mg	-2.74	-3.43	-2.05
insulin + on	empag 25	empag 10	-0.42	-0.93	0.09
insulin + on	empag 25	Canagliflozin 100mg	0.06	-0.71	0.83
insulin + on	empag 25	Canagliflozin 300mg	0.55	-0.23	1.31
insulin + on	empag 25	Dapagliflozin 5mg	-0.35	-1.08	0.38
insulin + on	empag 25	Dapagliflozin 10mg	0.26	-0.47	1
insulin + on	empag 25	Sitagliptin 100mg	ND	ND	ND
insulin + on	empag 10	empag 25	0.42	-0.09	0.93
insulin + on	empag 10	Canagliflozin 100mg	0.49	-0.25	1.22
insulin + on	empag 10	Canagliflozin 300mg	0.97	0.24	1.7
insulin + on	empag 10	Dapagliflozin 5mg	0.07	-0.64	0.77
insulin + on	empag 10	Dapagliflozin 10mg	0.67	-0.02	1.39
insulin + on	empag 10	Sitagliptin 100mg	ND	ND	ND

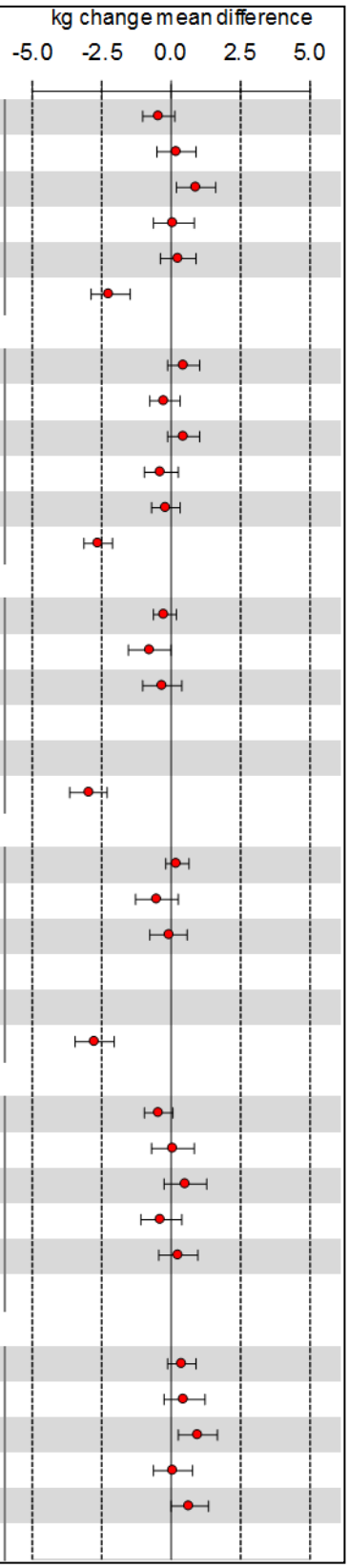

Figure 8 Summary of NMA results for mean change (mmHg) in SBP at 24 ± 4 weeks (values less than 0 indicates empagliflozin superior)

	empag	comparator	MD	LCI	UCI
Dual	empag 25	empag 10	-0.82	-3.86	2.11
Dual	empag 25	Canagliflozin 100mg	-0.96	-3.88	2.24
Dual	empag 25	Canagliflozin 300mg	0.34	-2.54	3.51
Dual	empag 25	Dapagliflozin 5mg	-2.87	-6.21	0.71
Dual	empag 25	Dapagliflozin 10mg	-1.27	-4.16	1.49
Dual	empag 25	Sitagliptin 100mg	-2.97	-7	1.1
Dual	empag 10	empag 25	0.82	-2.11	3.86
Dual	empag 10	Canagliflozin 100mg	-0.12	-3.74	3.73
Dual	empag 10	Canagliflozin 300mg	1.16	-2.37	5
Dual	empag 10	Dapagliflozin 5mg	-2.06	-5.8	2.09
Dual	empag 10	Dapagliflozin 10mg	-0.44	-3.96	2.98
Dual	empag 10	Sitagliptin 100mg	-2.19	-6.56	2.33
Triple	empag 25	empag 10	0.6	-1.36	2.55
Triple	empag 25	Canagliflozin 100mg	0.24	-3.07	3.46
Triple	empag 25	Canagliflozin 300mg	-0.35	-3.64	2.84
Triple	empag 25	Dapagliflozin 5mg	ND	ND	ND
Triple	empag 25	Dapagliflozin 10mg	ND	ND	ND
Triple	empag 25	Sitagliptin 100mg	-6.31	-10.1	-2.7
Triple	empag 10	empag 25	-0.6	-2.55	1.36
Triple	empag 10	Canagliflozin 100mg	-0.37	-3.63	2.88
Triple	empag 10	Canagliflozin 300mg	-0.94	-4.24	2.29
Triple	empag 10	Dapagliflozin 5mg	ND	ND	ND
Triple	empag 10	Dapagliflozin 10mg	ND	ND	ND
Triple	empag 10	Sitagliptin 100mg	-6.93	-10.61	-3.26
insulin + on	empag 25	empag 10	0.59	-1.12	2.31
insulin + on	empag 25	Canagliflozin 100mg	0.36	-3.08	3.81
insulin + on	empag 25	Canagliflozin 300mg	2.14	-1.34	5.6
insulin + on	empag 25	Dapagliflozin 5mg	0.13	-3.02	3.23
insulin + on	empag 25	Dapagliflozin 10mg	0.88	-2.33	3.98
insulin + on	empag 25	Sitagliptin 100mg	ND	ND	ND
insulin + on	empag 10	empag 25	-0.59	-2.31	1.12
insulin + on	empag 10	Canagliflozin 100mg	-0.26	-3.64	3.16
insulin + on	empag 10	Canagliflozin 300mg	1.55	-1.94	5.01
insulin + on	empag 10	Dapagliflozin 5mg	-0.45	-3.57	2.6
insulin + on	empag 10	Dapagliflozin 10mg	0.27	-2.87	3.38
insulin + on	empag 10	Sitagliptin 100mg	ND	ND	ND

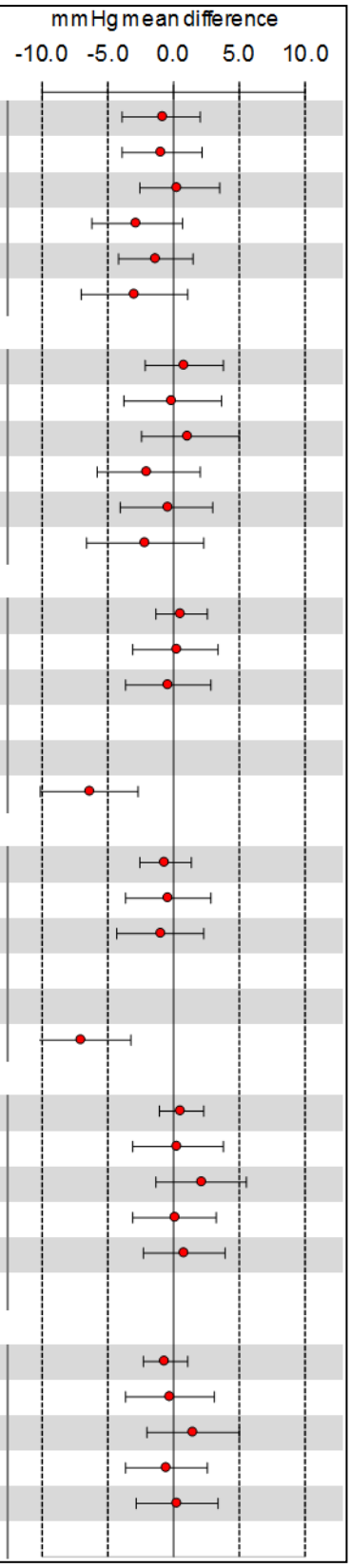

Table 1Summary of NMA results for dual therapy (in combination with thiazolidinedione)

Mean change in HbA1c, % (95% CrI)			
Intervention/ Comparator	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Dapagliflozin 10 mg**
Empagliflozin 25 mg	-0.12 (-0.51 to 0.27)	-	NA
Dapagliflozin 10 mg	0.00 (-0.45 to 0.44)	0.12 (-0.33 to 0.57)	NA
Sitagliptin 100 mg	0.35 (-0.01 to 0.71)	**0.47 (0.10 to 0.83)**	0.35 (-0.06 to 0.78)
Mean change in body weight, kg (95% CrI)			
Intervention/ Comparator	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Dapagliflozin 10 mg**
Empagliflozin 25 mg	0.01 (-1.20 to 1.22)	NA	NA
Dapagliflozin 10 mg	-0.43 (-1.86 to 1.01)	-0.44 (-1.85 to 0.98)	NA
Sitagliptin 100 mg	**1.87 (0.38 to 3.39)**	**1.86 (0.37 to 3.35)**	**2.30 (0.62 to 3.98)**
Mean change in SBP, mmHg (95% CrI)			
Intervention/ Comparator	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Dapagliflozin 10 mg**
Empagliflozin 25 mg	-4.32 (-9.08 to 0.55)	NA	NA
Dapagliflozin 10 mg	-2.06 (-8.10 to 3.80)	2.24 (-3.71 to 8.05)	NA
Sitagliptin 100 mg	NA	NA	NA
Hypoglycaemia RR (95% CrI) – overall, severe, non-severe			
	NA between these comparators		
UTIs, RR (95% CrI)			
Intervention/ Comparator	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Dapagliflozin 10 mg**
Empagliflozin 25 mg	1.34 (0.50 to 4.24)	NA	NA
Dapagliflozin 10 mg	0.15 (0.00 to 18.06)	0.10 (0.00 to 11.73)	NA
Sitagliptin 100 mg	0.15 (0.00 to 17.96)	0.11 (0.00 to 11.85)	NA
NA: Not available			

Table 2Summary of NMA results for triple therapy (in combination with metformin plus a thiazolidinedione)

Mean change in HbA1c, % (95% CrI)				
Intervention/ Comparator	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Canagliflozin 100 mg**	**Canagliflozin 300 mg**
Empagliflozin 25 mg	-0.15 (-0.36 to 0.06)	NA	NA	NA
Canagliflozin 100 mg	-0.19 (-0.49 to 0.10)	-0.04 (-0.32 to 0.24)	NA	NA
Canagliflozin 300 mg	**-0.33 (-0.61 to -0.06)**	-0.18 (-0.44 to 0.08)	-0.14 (-0.30 to 0.02)	NA
Sitagliptin 100 mg	-0.26 (-0.52 to 0.00)	-0.11 (-0.36 to 0.14)	-0.07 (-0.31 to 0.17)	NA
Mean change in body weight, kg (95% CrI)				
Intervention/ Comparator	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Canagliflozin 100 mg**	**Canagliflozin 300 mg**
Empagliflozin 25 mg	0.15 (-0.54 to 0.86)	NA	NA	NA
Canagliflozin 100 mg	-0.41 (-1.48 to 0.64)	-0.57 (-1.64 to 0.49)	NA	NA
Canagliflozin 300 mg	**-1.35 (-2.41 to -0.30)**	**-1.51 (-2.56 to -0.45)**	**-0.94 (-1.74 to -0.13)**	NA
Sitagliptin 100 mg	**2.33 (1.42 to 3.24)**	**2.18 (1.26 to 3.09)**	**2.75 (1.76 to 3.75)**	**3.69 (2.69 to 4.69)**
Mean change in SBP, mmHg (95% CrI)				
Intervention/ Comparator	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Canagliflozin 100 mg**	**Canagliflozin 300 mg**
Empagliflozin 25 mg	0.18 (-2.54 to 2.82)	NA	NA	NA
Canagliflozin 100 mg	0.10 (-3.87 to 4.13)	-0.05 (-4.02 to 3.93)	NA	NA
Canagliflozin 300 mg	0.69 (-3.29 to 4.68)	0.50 (-3.48 to 4.53)	0.59 (-2.39 to 3.55)	NA
Sitagliptin 100 mg	NA	NA	NA	NA
Hypoglycaemia, RR (95% CrI)				
Intervention/ Comparator	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Canagliflozin 100 mg**	**Canagliflozin 300 mg**
Empagliflozin 25 mg	2.4 (0.74 to 13.10)	NA	NA	NA
Canagliflozin 100 mg	0.17 (0.00 to 67.43)	0.07 (0.00 to 20.36)	NA	NA
Canagliflozin 300 mg	0.19 (0.00 to 69.34)	0.07 (0.00 to 19.62)	NA	NA
Sitagliptin 100 mg	2.13 (0.42 to 14.08)	0.90 (0.20 to 3.11)	NA	NA
Hypoglycaemia (non-severe), RR (95% CrI)				
Intervention/ Comparator	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Canagliflozin 100 mg**	**Canagliflozin 300 mg**
Empagliflozin 25 mg	3.18 (0.75 to 23.82)	NA	NA	NA

Canagliflozin 100 mg	NA	0.05 (0.00 to 44.10)	NA	NA
Canagliflozin 300 mg	NA	0.05 (0.00 to 44.64)	NA	NA
Sitagliptin 100 mg	NA	NA	NA	NA
Hypoglycaemia (severe), RR (95% CrI)				
	NA			
UTIs, RR (95% CrI)				
Intervention/ Comparator	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Canagliflozin 100 mg**	**Canagliflozin 300 mg**
Empagliflozin 25 mg	0.60 (0.28 to 1.11)	NA	NA	NA
Canagliflozin 100 mg	0.10 (0.00 to 11.31)	0.18 (0.00 to 21.79)	NA	NA
Canagliflozin 300 mg	0.11 (0.00 to 11.66)	0.19 (0.00 to 23.29)	NA	NA
Sitagliptin 100 mg	NA	NA	NA	NA
NA: Not available				

Appendix B: Supporting evidence

Related NICE guidance

Published

- Canagliflozin in combination therapy for treating type 2 diabetes. NICE technology appraisal guidance 315 (2014). Available from http://www.nice.org.uk/guidance/TA315
- Dapagliflozin in combination therapy for treating type 2 diabetes. NICE technology appraisal guidance 288 (2013). Available from http://www.nice.org.uk/guidance/TA288
- Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. NICE technology appraisal guidance 248 (2012). Available from http://www.nice.org.uk/guidance/TA248
- Liraglutide for the treatment of type 2 diabetes. NICE technology appraisal guidance 203 (2010). Available from www.nice.org.uk/guidance/TA203
- Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes (partial update of CG66) NICE clinical guideline 87 (2009) Available from www.nice.org.uk/guidance/CG87
- Type 2 diabetes: the management of type 2 diabetes (partially updated by CG87). NICE clinical guideline 66 (2008). Available from www.nice.org.uk/guidance/CG66
- Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. NICE clinical guideline 63 (2008). Available from www.nice.org.uk/guidance/CG63
- Continuous subcutaneous insulin infusion for the treatment of diabetes (review). NICE technology appraisal guidance 151 (2008). Available from www.nice.org.uk/guidance/TA151
- Type 2 diabetes: prevention and management of foot problems. NICE clinical guideline 10 (2004). Available from www.nice.org.uk/guidance/CG10

NICE pathways

- There is a NICE pathway on diabetes, which is available from http://pathways.nice.org.uk/pathways/diabetes

Appendix C: Previous NICE recommendations

Type 2 diabetes: the management of type 2 diabetes
NICE clinical guideline 87 (partial update of CG 66)

1.5 Oral glucose control therapies (1): metformin, insulin secretagogues and acarbose

1.5.1 Metformin

1.5.1.1 Start metformin treatment in a person who is overweight or obese (tailoring the assessment of body-weight-associated risk according to ethnic group[5]) and whose blood glucose is inadequately controlled (see 1.3.1) by lifestyle interventions (nutrition and exercise) alone.

1.5.1.2 Consider metformin as an option for first-line glucose-lowering therapy for a person who is not overweight.

1.5.1.3 Continue with metformin if blood glucose control remains or becomes inadequate (see 1.3.1) and another oral glucose-lowering medication (usually a sulfonylurea) is added.

1.5.1.4 Step up metformin therapy gradually over weeks to minimise risk of gastrointestinal side effects. Consider a trial of extended-absorption metformin tablets where gastrointestinal tolerability prevents continuation of metformin therapy.

1.5.1.5 Review the dose of metformin if the serum creatinine exceeds 130 micromol/litre or the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73-m^2.

- Stop the metformin if the serum creatinine exceeds 150 micromol/litre or the eGFR is below 30 ml/minute/1.73-m^2.
- Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73-m^2.

[5] See 'Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children' (NICE clinical guideline 43) (www.nice.org.uk/guidance/CG43).

1.5.1.6 The benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that:

- due consideration can be given to the cardiovascular-protective effects of the drug
- an informed decision can be made on whether to continue or stop the metformin.

1.5.2 Insulin secretagogues

1.5.2.1 Consider a sulfonylurea as an option for first-line glucose-lowering therapy if:

- the person is not overweight
- the person does not tolerate metformin (or it is contraindicated) **or**
- a rapid response to therapy is required because of hyperglycaemic symptoms.

1.5.2.2 Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate (see 1.3.1) with metformin.

1.5.2.3 Continue with a sulfonylurea if blood glucose control remains or becomes inadequate (see 1.3.1) and another oral glucose-lowering medication is added.

1.5.2.4 Prescribe a sulfonylurea with a low acquisition cost (but not glibenclamide) when an insulin secretagogue is indicated (see 1.5.2.1 and 1.5.2.2).

1.5.2.5 When drug concordance is a problem, offer a once-daily, long-acting sulfonylurea.

1.5.2.6 Educate a person being treated with an insulin secretagogue, particularly if renally impaired, about the risk of hypoglycaemia.

1.5.3 Rapid-acting insulin secretagogues

1.5.3.1 Consider offering a rapid-acting insulin secretagogue to a person with an erratic lifestyle.

1.5.4 Acarbose

1.5.4.1 Consider acarbose for a person unable to use other oral glucose-lowering medications.

1.6 Oral glucose control therapies (2): other oral agents and exenatide

The recommendations in this section were updated by the short clinical guideline 'Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes' (www.nice.org.uk/CG87shortguideline). The guideline gives details of the methods and the evidence used to develop the recommendations.

1.6.1 DPP-4 inhibitors (sitagliptin, vildagliptin)

1.6.1.1 Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 6.5%, or other higher level agreed with the individual) if:

- the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or
- the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated. ***[new 2009]***

1.6.1.2 Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 6.5%, or other higher level agreed with the individual) if:

- the person does not tolerate metformin, or metformin is contraindicated. ***[new 2009]***

1.6.1.3 Consider adding sitagliptin[6] as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 7.5% or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[7]. ***[new 2009]***

1.6.1.4 Only continue DPP-4 inhibitor therapy (sitagliptin, vildagliptin) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA_{1c} in 6 months). ***[new 2009]***

1.6.1.5 Discuss the potential benefits and risks of treatment with a DPP-4 inhibitor (sitagliptin, vildagliptin) with the person to enable them to make an informed decision.

A DPP-4 inhibitor (sitagliptin, vildagliptin) may be preferable to a thiazolidinedione (pioglitazone) if:

- further weight gain would cause or exacerbate significant problems associated with a high body weight, or
- a thiazolidinedione (pioglitazone) is contraindicated, or
- the person has previously had a poor response to, or did not tolerate, a thiazolidinedione (pioglitazone).

There may be some people for whom either a DPP-4 inhibitor (sitagliptin, vildagliptin) or a thiazolidinedione (pioglitazone) may be suitable and, in this case, the choice of treatment should be based on patient preference. ***[new 2009]***

[6] At the time of publication, sitagliptin was the only DPP-4 inhibitor with UK marketing authorisation for use in this combination.

[7] Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

1.6.2 Thiazolidinediones (pioglitazone)[8]

1.6.2.1 Consider adding a thiazolidinedione (pioglitazone) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 6.5%, or other higher level agreed with the individual) if:

- the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or
- a person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated. ***[new 2009]***

1.6.2.2 Consider adding a thiazolidinedione (pioglitazone) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 6.5%, or other higher level agreed with the individual) if:

- the person does not tolerate metformin or metformin is contraindicated. ***[new 2009]***

1.6.2.3 Consider adding a thiazolidinedione (pioglitazone) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 7.5%, or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[9]. ***[new 2009]***

1.6.2.4 Do not commence or continue a thiazolidinedione (pioglitazone) in people who have heart failure, or who are at higher risk of fracture. ***[new 2009]***

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[8] The recommendations in this section replace 'Guidance on the use of glitazones for the treatment of type 2 diabetes' (NICE technology appraisal guidance 63).

[9] Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

1.6.2.5 When selecting a thiazolidinedione (pioglitazone), take into account up-to-date advice from the relevant regulatory bodies (the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency), cost, safety and prescribing issues (see 1.6.2.8). ***[new 2009]***

1.6.2.6 Only continue thiazolidinedione therapy (pioglitazone) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA_{1c} in 6 months). ***[new 2009]***

1.6.2.7 Consider combining pioglitazone with insulin therapy[10] for a person:

- who has previously had a marked glucose-lowering response to thiazolidinedione therapy (pioglitazone), or
- who is on high-dose insulin therapy and whose blood glucose is inadequately controlled. ***[new 2009]***

1.6.2.8 Discuss the potential benefits and risks of treatment with a thiazolidinedione (pioglitazone) with the person to enable them to make an informed decision.

A thiazolidinedione (pioglitazone) may be preferable to a DPP-4 inhibitor (sitagliptin, vildagliptin) if:

- the person has marked insulin insensitivity, or
- a DPP-4 inhibitor (sitagliptin, vildagliptin) is contraindicated, or
- the person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor (sitagliptin, vildagliptin).

There may be some people for whom either a thiazolidinedione (pioglitazone) or a DPP-4 inhibitor (sitagliptin, vildagliptin) may be suitable and, in this case, the choice of treatment should be based on patient preference. ***[new 2009]***

[10] At the time of publication pioglitazone was the only thiazolidinedione with UK marketing authorisation for use with insulin.

1.6.3 GLP-1 mimetic (exenatide)

1.6.3.1 Consider adding a GLP-1 mimetic (exenatide) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 7.5%, or other higher level agreed with the individual), and the person has:

- a body mass index (BMI) ≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or
- a BMI < 35.0 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. ***[new 2009]***

1.6.3.2 Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA_{1c} and a weight loss of at least 3% of initial body weight at 6 months). ***[new 2009]***

1.6.3.3 Discuss the potential benefits and risks of treatment with a GLP-1 mimetic (exenatide) with the person to enable them to make an informed decision. ***[new 2009]***

1.7 Glucose control: insulin therapy

1.7.1 Oral agent combination therapy with insulin

1.7.1.1 When starting basal insulin therapy:

- continue with metformin and the sulfonylurea (and acarbose, if used)
- review the use of the sulfonylurea if hypoglycaemia occurs.

1.7.1.2 When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):

- continue with metformin
- continue the sulfonylurea initially, but review and discontinue if hypoglycaemia occurs.

1.7.2 Insulin therapy

The recommendations in this section were updated by the short clinical guideline 'Type 2 diabetes newer agents for blood glucose control in type 2 diabetes' (www.nice.org.uk/CG87shortguideline). The guideline gives details of the methods and the evidence used to develop the recommendations.

1.7.2.1 Discuss the benefits and risks of insulin therapy when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 7.5% or other higher level agreed with the individual) with other measures. Start insulin therapy if the person agrees. ***[new 2009]***

1.7.2.2 For a person on dual therapy who is markedly hyperglycaemic, consider starting insulin therapy in preference to adding other drugs to control blood glucose unless there is strong justification[11] not to. ***[new 2009]***

1.7.2.3 When starting insulin therapy, use a structured programme employing active insulin dose titration that encompasses:

- structured education
- continuing telephone support
- frequent self-monitoring
- dose titration to target
- dietary understanding
- management of hypoglycaemia
- management of acute changes in plasma glucose control
- support from an appropriately trained and experienced healthcare professional.

1.7.2.4 Initiate insulin therapy from a choice of a number of insulin types and regimens.

[11] Because of employment, social or recreational issues related to putative hypoglycaemia, injection anxieties, other personal issues or obesity.

- Begin with human NPH insulin injected at bed-time or twice daily according to need.
- Consider, as an alternative, using a long-acting insulin analogue (insulin detemir, insulin glargine) if:
  - the person needs assistance from a carer or healthcare professional to inject insulin, and use of a long-acting insulin analogue (insulin detemir, insulin glargine) would reduce the frequency of injections from twice to once daily, or
  - the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or
  - the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs, or
  - the person cannot use the device to inject NPH insulin.
- Consider twice-daily pre-mixed (biphasic) human insulin (particularly if $HbA_{1c} \geq 9.0\%$). A once-daily regimen may be an option.
- Consider pre-mixed preparations that include short-acting insulin analogues, rather than pre-mixed preparations that include short-acting human insulin preparations, if:
  - a person prefers injecting insulin immediately before a meal, or
  - hypoglycaemia is a problem, or
  - blood glucose levels rise markedly after meals. ***[new 2009]***

1.7.2.5 Consider switching to a long-acting insulin analogue (insulin detemir, insulin glargine) from NPH insulin in people:

- who do not reach their target HbA_{1c} because of significant hypoglycaemia, or
- who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA_{1c} reached, or
- who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made, or

- who need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections. ***[new 2009]***

1.7.2.6 Monitor a person on a basal insulin regimen (NPH insulin or a long-acting insulin analogue [insulin detemir, insulin glargine]) for the need for short-acting insulin before meals (or a pre-mixed insulin preparation). ***[new 2009]***

1.7.2.7 Monitor a person who is using pre-mixed insulin once or twice daily for the need for a further injection of short-acting insulin before meals or for a change to a regimen of mealtime plus basal insulin, based on NPH insulin or long-acting insulin analogues (insulin detemir, insulin glargine), if blood glucose control remains inadequate. ***[new 2009]***

1.7.3 Insulin delivery devices

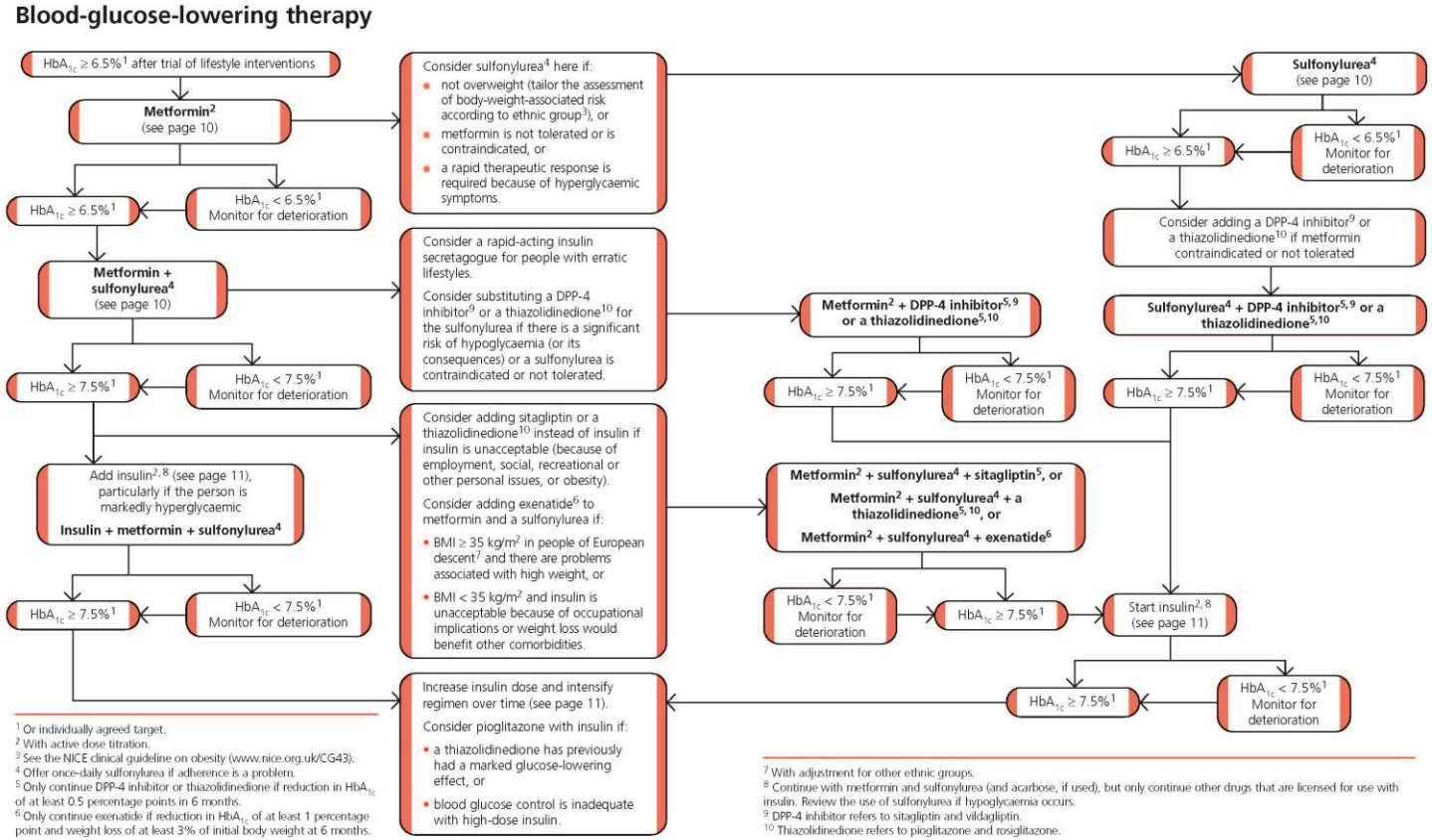
1.7.3.1 Offer education to a person who requires insulin about using an injection device (usually a pen injector and cartridge or a disposable pen) that they and/or their carer find easy to use.

1.7.3.2 Appropriate local arrangements should be in place for the disposal of sharps.

1.7.3.3 If a person has a manual or visual disability and requires insulin, offer a device or adaptation that:

- takes into account his or her individual needs
- he or she can use successfully.

Care pathway from short clinical guideline 87 (page numbers refer to the quick reference guide for CG87)



Liraglutide for the treatment of type 2 diabetes mellitus

NICE technology appraisal guidance 203

1.1 Liraglutide 1.2 mg daily in triple therapy regimens (in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended as an option for the treatment of people with type 2 diabetes, only if used as described for exenatide in 'Type 2 diabetes: the management of type 2 diabetes' (NICE clinical guideline 87); that is, when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual), and the person has:

- a body mass index (BMI) ≥ 35 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, **or**
- a BMI < 35 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

1.2 Treatment with liraglutide 1.2 mg daily in a triple therapy regimen should only be continued as described for exenatide in 'Type 2 diabetes: the management of type 2 diabetes' (NICE clinical guideline 87); that is, if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA1c and a weight loss of at least 3% of initial body weight at 6 months).

1.3 Liraglutide 1.2 mg daily in dual therapy regimens (in combination with metformin or a sulphonylurea) is recommended as an option for the treatment of people with type 2 diabetes, only if:

- the person is intolerant of either metformin **or** a sulphonylurea, or treatment with metformin **or** a sulphonylurea is contraindicated, **and**
- the person is intolerant of thiazolidinediones **and** dipeptidyl peptidase-4 (DPP-4) inhibitors, or treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.

1.4 Treatment with liraglutide 1.2 mg daily in a dual therapy regimen should only be continued if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in HbA1c at 6 months).

1.5 Liraglutide 1.8 mg daily is not recommended for the treatment of people with type 2 diabetes.

1.6 People with type 2 diabetes currently receiving liraglutide who do not meet the criteria specified in section 1.1 or 1.3, or who are receiving liraglutide 1.8 mg, should have the option to continue their current treatment until they and their clinicians consider it appropriate to stop.

Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes

NICE technology appraisal guidance 248

1.1 Prolonged-release exenatide in triple therapy regimens (that is, in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended as a treatment option for people with type 2 diabetes as described in 'Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87); that is, when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 7.5% [59 mmol/mol] or other higher level agreed with the individual), and the person has:

- a body mass index (BMI) ≥ 35 kg/m^2 in those of European family origin (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight **or**
- a BMI < 35 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

1.2 Treatment with prolonged-release exenatide in a triple therapy regimen should only be continued as described in 'Type 2 diabetes: the management of type 2 diabetes' (NICE clinical guideline 87); that is, if a beneficial metabolic response has been shown (defined as a reduction of

at least 1 percentage point in HbA_{1c} [11 mmol/mol] and a weight loss of at least 3% of initial body weight at 6 months).

1.3 Prolonged-release exenatide in dual therapy regimens (that is, in combination with metformin or a sulphonylurea) is recommended as a treatment option for people with type 2 diabetes, as described in 'Liraglutide for the treatment of type 2 diabetes mellitus' (NICE technology appraisal 203); that is, only if:

- the person is intolerant of either metformin **or** a sulphonylurea, or a treatment with metformin **or** a sulphonylurea is contraindicated, **and**
- the person is intolerant of thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors, **or** a treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.

1.4 Treatment with prolonged-release exenatide in a dual therapy regimen should only be continued as described in 'Liraglutide for the treatment of type 2 diabetes mellitus' (NICE technology appraisal guidance 203); that is, if a beneficial metabolic response has been

Dapagliflozin in combination therapy for treating type 2 diabetes

NICE technology appraisal guidance 288

1.1 Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87).

1.2 Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

1.3 Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes, except as part of a clinical trial.

1.4 People currently receiving dapagliflozin in a dual or triple therapy regimen that is not recommended for them in 1.1 or 1.3 should be able to continue treatment until they and their clinician consider it appropriate to stop.

Canagliflozin in combination therapy for treating type 2 diabetes

NICE technology appraisal guidance 315

1.1 Canagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- a sulfonylurea is contraindicated or not tolerated or
- the person is at significant risk of hypoglycaemia or its consequences.

1.2 Canagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:

- metformin and a sulfonylurea or
- metformin and a thiazolidinedione.

1.3 Canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

1.4 People currently receiving canagliflozin in a dual or triple therapy regimen that is not recommended for them in by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

Appendix D: Clinical efficacy section of the European public assessment report

The section 2.5 of the European public assessment report (pages 37–66) details the clinical efficacy of the empagliflozin.