Lead team presentation Dapagliflozin in triple therapy regimens for treating type 2 diabetes (part-review of TA288) – STA

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee A

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Summary of this appraisal

- Partial review: dapagliflozin already recommended for other indications but not in triple therapy (no evidence available previously). Other SGLT2 inhibitors already recommended in triple therapy
- Company did not evaluate as add on to metformin and DPP4 inhibitor (scope), only metformin plus sulfonylurea
- Compared dapagliflozin added to metformin plus sulfonylurea with other SGLT2 inhibitors and DPP4 inhibitors (not injectables or pioglitazone), using NMA,
- NMA included only one trial for dapagliflozin, and NMA results not all consistent with trial results
- Weight loss benefit, but uncertain for how long it lasts
- Company assumes stop dapagliflozin once insulin started
- Costs the same as other SGLT2 inhibitors, but more than DPP4 inhibitors
- Company base case estimates that dapagliflozin dominates DPP4 inhibitors (cheaper and more effective) except in some scenarios e.g. different risk equations used for complications or dapagliflozin continued long term alongside insulin
- ERG estimate higher costs, and marginal QALY gain for dapagliflozin-compared with DPP4 inhibitors (ICER >30 k/QALY)

Type 2 diabetes disease background

- Progressive, chronic metabolic disorder leading to high levels of blood glucose. It develops when
  - the body becomes resistant to insulin
  - there is a loss of insulin production in the pancreas
- Diagnoses in England have doubled over past 20 years
- Approximately 2.8 million people living in England diagnosed with diabetes (2014)
- Around 90% of diabetes is type 2
- Can be associated with increased age and weight, and family origin (more common in people of South Asian, African and Caribbean family origin)

Type 2 diabetes health consequences

Elevated blood glucose is associated with:

- Macrovascular complications:
  - Arterial disease: coronary heart disease, cerebrovascular disease and peripheral arterial disease.
- Microvascular complications:
  - Eye disease (leading cause of blindness)
  - Kidney disease (leading cause of dialysis/transplantation)
  - Foot problems (ulcers/amputation)
  - Neuropathy (sensory loss/pain/gastric paralysis/other)
  - Erectile dysfunction (impotence)
- Other risk factors for cardiovascular disease including obesity, hypertension, lipid disorders cluster:
  - Premature death – life expectancy reduced by up to 10 years
  - Significant direct cost to the NHS (direct care £23.7 billion) and indirect costs to society

Many of these complications delayed/prevented by lowering blood glucose

Treatment pathway (metformin tolerant)

Dietary advice and increasing physical activity (NG28)

If blood glucose is not adequately controlled by lifestyle interventions alone:

Monotherapy	Metformin (NG28)
1st intensification	Metformin plus either: DPP4 inhibitor, pioglitazone, sulfonylurea (SU), or SGLT2 inhibitor* (NG28, TA288, TA315, TA336)
2nd intensification	**Metformin plus either: DPP4 inhibitor + SU; pioglitazone + SU; pioglitazone + SGLT2 inhibitor**; SU + SGLT2 inhibitor** (NG28, TA315 + TA336)**

*At 1st intensification SGLT2 inhibitors include canagliflozin, dapagliflozin, empagliflozin

**At 2nd intensification, SGLT2 inhibitors include canagliflozin or empagliflozin only. This appraisal will consider dapagliflozin at this point in the pathway

Related technology appraisals

- TA390 (2016) ‘Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes’.
  - All 3 treatments recommended as monotherapy when metformin is not appropriate
- TA336 (2015) ‘Empagliflozin in combination therapy for treating type 2 diabetes’.
  - Recommended as **dual** and **triple** therapy
- TA315 (2014) ‘Canagliflozin in combination therapy for treating type 2 diabetes’.
  - Recommended as **dual** and **triple** therapy
- TA288 (2013) ‘Dapagliflozin in combination therapy for treating type 2 diabetes’.
  - Recommended as **dual therapy**;
  - The **triple therapy** regimen (in combination with metformin and a sulfonylurea) is not recommended except as part of a clinical trial
  - The triple therapy recommendation will be reconsidered in this part-review of TA288

Patient perspective (1): Outlook

- Diabetes is progressive
- Initial symptoms: increased thirst, urinating more, tiredness, slow healing wounds, blurred vision
- Patients move to medication to control blood sugar levels after trying lifestyle changes like diet and more exercise
- If not controlled longer term diabetes complications include:
  - Amputations
  - Blindness
  - Cardiovascular problems
  - Renal problems
  - Strokes
- Adverse effects of treatment include urinary and genital tract infections
- Inevitably there is huge uncertainty and anxiety for people with type 2 diabetes and their families

Patient perspective (2): What patients would like

- Early diagnosis and effective treatment to improve health related quality of life and duration of life
- Clinicians with a range of options to tailor treatment to patient's short term needs and long term interests
  - Adequately control blood glucose
  - Minimise number and severity of hypos
  - Switch treatments if a drug is not tolerated
  - Minimise risk of long term complications
  - Minimise risk of treatment adverse events
- Accurate and balanced information and advice to help people with type 2 diabetes, their families and carers manage the impact of the disease and the treatment adverse events

Dapagliflozin

- Selective sodium glucose-co-transporter 2 (SGLT-2) inhibitor
- Blocks glucose reabsorption in kidneys & promotes excretion of excess glucose
- Acts through an insulin independent mechanism
- Improves glycaemic control, and can reduce blood pressure and weight
- 10mg once daily oral tablet

Marketing authorisation:

- "indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control 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.
  - Add-on combination therapy In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control

Decision problem

	Final scope	Company approach	Company comments	ERG
Pop.	Adults, T2DM not controlled on dual therapy with MET + SU or DPP4i	Adults, T2DM not controlled on dual therapy with MET+SU	Not enough evidence for MET + DPP4i	Triple therapy with SGLT2i+ DPP4i would cost >£900
Int.	Dapagliflozin in combination with 2 other oral anti-diabetic agents			
Com.	The following with 2 other oral agents: other SGLT2i; DPP4i; pioglitazone; GLP-1; SU; insulin	MET + SU with: DPP4i; canagliflozin; empagliflozin	Pioglitazone rarely used; Insulin/GLPs used later in pathway (injectables)	Disagree re. pioglitazone (>1 million prescriptions) Agree re injectables
Out.	Mortality; complications of diabetes, HbA1c; BMI; hypoglycaemia; CV risk; adverse effects of treatment; HRQL	HbA1c; weight; systolic blood pressure, hypoglycaemia, adverse effects.	Trials did not typically report data for long-term outcomes	Agree

Clinical evidence

- Company excluded population with disease not adequately controlled on metformin + DPP4 inhibitor because not enough evidence to do comparisons
- Company noted following re comparators:
  - SGLT2 inhibitors: “pragmatic” case for all 3 SGLT2 inhibitors to have same recommendation (all have same costs and similar effectiveness, yet dapagliflozin is only SGLT2 not recommended for triple)
  - Injectables: insulin/GLP1s not typically used before orals because of additional expense and requirement to inject; therefore excluded
  - Pioglitazone: Rarely used; therefore excluded
- Company identified 1 relevant randomised phase III controlled trial ‘Study 5’ (n=219). Dapagliflozin vs placebo, both when added on to metformin + sulfonylurea
  - 24 weeks, with 28 week extension
  - 46 centres across several European countries (not UK) and Canada.
  - Treatments balanced for baseline characteristics
  - Primary outcome: mean change in HbA1c
- Company also presented NMA and observational evidence

Study 5 outcomes (bold = p<0.05 vs placebo [where reported])

		Dapagliflozin (n=108)	Placebo (n=108)
Mean change from baseline HbA1c (%)			
Week 24	Change (95% CI)	**-0.86 (-1.00, -0.72)**	-0.17 (-0.31, -0.02)
Week 52	Change (95% CI)	-0.8 (-1.0, -0.6)	-0.1 (-0.3, 0.1)
Mean change from baseline body weight (kg)			
Week 24		**-2.65 (-3.16, -2.14)**	-0.58 (-1.09, -0.07)
Week 52	Change (95% CI)	-2.9 (-3.6, -2.2)	-1.0 (-1.8, -0.1)
Mean change from baseline fasting plasma glucose (mg/dL)			
Week 24	Change (95% CI)	**-34.23 (-40.98, -27.48)**	-0.78 (-7.56, 6.01)
Week 52	Change (95% CI)	−1.5 (−1.9, −1.1)	0.6 (0.1, 1.1)
Mean change from baseline seated systolic blood pressure (mmHg)			
Week 8	Change (95% CI)	**-4.04 (-6.36, -1.72)**	-0.27 (-2.60, 2.05)
Week 52	Change (95% CI)	-1.0 (-3.6, 1.6)	1.1 (-2.2, 4.5)

Study 5 quality of life data

- EQ5D:
  - No statistically significant differences v placebo, both groups almost maintained index score from week 0 to 24
- Impact of Weight on Quality of Life-Lite and Diabetes Treatment Satisfaction Questionnaire:
  - No statistically significant difference vs placebo ($p>0.20$)
  - In both arms scores improved from baseline to week 52
- SHIELD Weight Questionnaire-9 (WQ-9):
  - Numerically greater proportion of dapagliflozin group reported improvement in all nine SHIELD WQ-9 items, and difference was statistically significant for physical health ($p=0.017$)
  - Over 52 weeks, patients maintained health status and health related quality of life when dapagliflozin was added to the treatment

Network meta-analysis (NMA) – dapagliflozin vs treatment

	HbA1c (mean difference)	Weight (mean difference)	SBP (mean difference)	Any hypoglycaemic event (odds ratio)
DPP4i	-0.06 (-0.43, 0.33)	**-2.33 (-4.17, -0.49)**	-4.96 (-17.82, 8.41)	1.14 (0.48, 2.92)
CANA300	0.24 (-0.19, 0.64)	-0.14 (-2.3, 2.02)	1.05 (-9.27, 11.65)	0.96 (0.39, 2.5)
CANA100	0.02 (-0.44, 0.44)	-0.42 (-2.78, 1.95)	1.67 (-8.78, 12.07)	0.97 (0.38, 2.59)
EMPA10	0 (-0.51, 0.52)	-0.2 (-2.46, 2.04)	0.06 (-11.36, 11.78)	1.68 (0.63, 4.67)
EMPA25	0 (-0.52, 0.52)	-0.1 (-2.33, 2.15)	0.19 (-11.31, 11.92)	1.46 (0.55, 4.01)
Placebo	**-0.7 (-1.06, -0.34**)	**-1.9 (-3.61, -0.18)**	-2.04 (-10.51, 6.45)	2.09 (0.9, 5.19)
Bold = statistically significant				

Adverse events

- Adverse events of interest were urinary and genital tract infections (because SGLT2 inhibitor mechanism of action of increasing urinary glucose may promote microbial growth) and hypoglycaemia:
  - Hypoglycaemia: low incidence and no major events
  - UTIs and GTIs: increased but modest incidence, and mild or moderate severity
- Cardiac event meta-analysis (21 trials, n=9,000+)
  - Dapagliflozin was not associated with increased risk of cardiovascular events for a composite of cardiovascular death, myocardial infarction, stroke and hospitalisation for unstable angina
- No statistically significant increases in risk of malignancy between dapagliflozin and control group
- US Food and Drug Administration (FDA) to issued a recently “strengthened” warning that health professionals should consider if any factors that would predispose patients to acute kidney injury before starting canagliflozin or dapagliflozin (warning did not include empagliflozin), after 101 cases (73 canagliflozin, 28 dapagliflozin) of which 4 died

Evidence Review Group's critique

Trial data

- 'Study 5': good quality trial, dapagliflozin improves glycaemic control and weight loss vs placebo. But company could have provided more data by extracting data from subgroups of other trials
- Not all comparators included:
  - Injectables: Exclusion appropriate. People will try orals first
  - Pioglitazone: Exclusion inappropriate. Although use has declined (concerns about adverse events), 2015 Prescription Cost Analysis data for England shows >1 million prescriptions

NMA data

- Limited data for some analyses
- NMA results inconsistent with trial data (treatments generally had more favourable outcomes in NMA than suggested by trial/s) In its model, ERG replaced several company NMA effectiveness assumptions with trial data

Key clinical issues for consideration

- The scope included people whose disease was not controlled on metformin and sulfonylurea **and** people whose disease was not controlled on metformin and DPP4 inhibitors. The company excluded the latter population. Is this appropriate?
- What are the main comparators for dapagliflozin in triple therapy? The company excluded the injectable treatments and pioglitazone (because it stated pioglitazone was rarely used in clinical practice). Are these exclusions appropriate?
- The ERG stated that the company could have included more relevant clinical trial data from the subgroups of other trials and some of the results of the network meta-analysis were not consistent with the individual trial data feeding into the network. Are the results of the company network meta-analysis plausible?
- How long does the weight loss last?
- How long will people remain on SGLT2 inhibitors?
- Are the efficacy and side effect profiles of the SGLT2 inhibitors sufficiently similar for them to be regarded as a class?
- Are DPP4 inhibitors the main comparators?