For committee, public and projector

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

1st Appraisal Committee meeting

Cost Effectiveness

Committee A

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ERG: Warwick Evidence

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Cardiff Diabetes Model

- Patient-level stochastic simulation model
- Risk factor and disease progression modelled through UK Prospective Diabetes Study (UKPDS) equations. Company used UKPDS68*
- Initial specification of age, sex, ethnicity, smoking status, duration of diabetes
- Modifiable risk factors (HbA1c, systolic blood pressure, cholesterol and weight) are updated according to treatment and natural progression after each cycle
- Model predicts
  - micro- and macro-vascular events: amputation, nephropathy, blindness, ischaemic heart disease, myocardial infarction, stroke, and congestive heart failure;
  - hypoglycaemia and other adverse events; and
  - death (cardiovascular and non-cardiovascular)

**Updated UKPDS82 event equations now available.*

Model assumptions

- All patients entered model with type 2 diabetes not controlled on dual therapy with metformin + sulfonylurea
- Received addition of either DPP4 inhibitors (as a class) or SGLT2 inhibitors (dapagliflozin, canagliflozin 100mg/300mg or empagliflozin 10mg/25mg)
- Treatment determined the evolution of risk factors HbA1c, systolic blood pressure, weight, and cholesterol levels
- Risk factors worsen over time; HbA1c >7.5% triggers next treatment
- Patients received set treatment sequence. After triple therapy, patients first switch to metformin/insulin, followed by (for the remainder of the model) metformin/intensified (50% increase) insulin
- Time horizon 40 years, cycle length 6 months, discount rate 3.5%

Clinical inputs (1)

- Treatment effect of interventions taken from:
  - Network meta-analysis (NMA): for HbAc1/weight/systolic blood pressure for all treatments (other than metformin plus insulin/intensified insulin, taken from literature)
  - Canagliflozin trial data: for severe hypoglycaemia, UTIs and GTIs for all treatments
- No treatment effect assumed for cholesterol
- Initial changes of weight from treatment only maintained for one year
- Treatment effect for outcomes worsened over time (using UKPDS68, other than for weight, where 0.1kg per year weight gain assumed)
- UKPDS68 used for all-cause mortality, and for 10 year risk of micro- or macro-vascular events in the model, which also varied over time according to patient age, duration of diabetes, gender, ethnicity, smoking status, and intermediate outcomes (HbA1c etc.)

Clinical inputs (2)

	Change from baseline			Prob. Disc.	No. of hypo (sympt)	Prob. Hypo (severe)	Prob. UTI	Prob. GI
	HbA1c (%)	Weight (kg)	SBP (mmHg)					
DPP4i	-0.79	0.12	1.85	0.029	0.181	0.034	0.021	0.056
Dapa	-0.85	-2.20	-3.13	0.053	0.202	0.040	0.119	0.040
Empa 10	-0.85	-2.10	-3.30	0.053	0.148	0.040	0.119	0.040
Empa 25	-0.85	-2.00	-3.19	0.053	0.131	0.040	0.119	0.040
Cana 100	-0.87	-1.78	-4.82	0.053	0.208	0.040	0.119	0.040
Cana 300	-1.09	-2.06	-4.16	0.053	0.208	0.040	0.119	0.040
Metformin + insulin	-1.10	1.08	0.00+	0	0.011	0.037	0	0
Intensified insulin	-1.11	1.90	0.00+	0	0.616	0.022	0	0

Utility values (1)

- Patients entered model with baseline utility 0.87, based on person aged 61 with type 2 diabetes and no complications.
- Baseline utility declined with age, based on EQ5D data by age.
- Patients experienced event-specific utility decrements, additive if >1 event
- For complication events (micro and macrovascular health states) the disutility was applied in cycle of the event and all cycles thereafter, whereas for adverse events (hypoglycaemia and urinary and genital tract infections) disutility was only applied in event cycle.
- Change in utility was assumed when there were changes in body weight.

Utility values (2)

	Utility	Source:
Ischemic Heart Disease	-0.090	UKPDS62
Myocardial infarction	-0.055	
Congestive Heart Failure	-0.108	
Stroke	-0.164	
Blindness	-0.074	
Amputation	-0.280	
End stage renal disease	-0.263	Currie (2005), using HODAR, Welsh T2DM database
For each unit change in BMI	±0.0061	Bagust (2005), observational database (n=4,600) using TTO
UTI	-0.00283	Barry (1997), cost-utility study of office-based strategies
GI	-0.00283	
Hypoglycaemic event	Not stated	Currie (2006), statistical model for fear of hypoglycaemia (n=1,305)
Key: HODAR: health outcomes data repository; TTO: time trade off		

Resource use and costs

Table: Annual drug costs	
SGLT2i (all)	£477
DPP4i (weighted average)	£425
Sulfonylurea (Gliclazide)	£30
Metformin	£25
Insulin	£181
Intensified insulin	£269

- Insulin applied as cost per day
- SGLT2 inhibitors assumed to accrue costs of renal monitoring
- No administration costs (all self-administered)

Table: Complications costs			
Event	**Fatal**	**Non-fatal**	**Maintenance**
No complication	NA	£465	NA
Ischaemic heart disease	NA	£3,346	£1,105
Myocardial infarction	£1,695	£6,451	£1,062
Congestive heart failure	£3,731	£3,731	£1,308
Stroke	£4,977	£3,946	£746
Amputation	£12,847	£12,847	£742
Blindness	NA	£1,685	£714
End stage renal disease	£35,715	£35,715	£35,631

Results (updated after clarification)

- Company identified errors which had minor impacts on 'original base case'. Only results after clarification ('base case A') are presented
- Company noted small cost and QALY differences, made ICERs unstable

Treatment	Costs (£)	QALYs	ICER (£/QALY)
Absolute results (per patient)			
Dapa	20,910	9.62	
DPP4-i	21,028	9.58	
Cana 100mg	20,844	9.62	
Cana 300mg	21,096	9.61	
Empa 10mg	20,899	9.61	
Empa 25mg	20,902	9.61	
Incremental results (per patient) (Dapa vs treatment)			
DPP4-i	-118	0.032	Dapa dominates
Cana 100mg	66	-0.001	Cana100 dominates
Cana 300mg	-187	0.003	Dapa dominates
Empa 10mg	10	0.005	£1,965
Empa 25mg	8	0.006	£1,354

Sensitivity and scenario analyses

Using ‘original base case’, company presented various scenario and deterministic sensitivity analyses (vs DPP4 inhibitors only) and probabilistic sensitivity analyses

- Scenario analyses included varying patient characteristics and HbA1c
  - In all results, dapagliflozin either remained dominant, or ICERs <£20,000 (max ICER £13,514, when changing assumptions for 2nd/3rd line drug costs)
- Univariate sensitivity analyses
  - results most sensitive to assumptions about smoking status (only ICER >£30,000), baseline hbA1c and age.
- Probabilistic sensitivity analyses
  - At max ICER of £20,000, dapagliflozin had probability of cost effectiveness of approx. 50% vs other SGLT2 inhibitors, and 56.98% vs DPP4 inhibitors.
- Company did not repeat original sensitivity/scenario analyses for ‘base case A’, as changes were negligible; it presented additional scenarios (including different baseline utility/%smokers/UKPDS assumptions), dapagliflozin remained dominant or cost-effective in majority of scenarios

Evidence Review Group (ERG) comments

- Model has been used for previous appraisals, but ERG unable to validate all analyses because it lacks transparency and takes a long time to run.
- Error in model in switching therapies: when HbA1c >7.5%, people remained on dapagliflozin for 1 cycle before next treatment, whereas DPP4s remained for 2 cycles. This may exaggerate differences in treatment costs.
- Weight loss assumption (maintained for 1 year) was pessimistic – evidence it is maintained at 2 years (Fioretto et al., 2016)
- Company used older UKPDS68 equations for incidence of complications, but UKPDS82 has more follow up data and predicts less incidence of myocardial infarction, renal failure and deaths. This will disadvantage less effective treatment (DPP4 inhibitors)
- UKPDS cost equations had been based on an older version (UKPDS65), rather than using the more recent data available (UKPDS84)
- Company assumed patients ceased orals when intensifying to insulin, however patients usually retain them in clinical practice
- Intensified insulin would not just be 50% increase as assumed by company; ERG assumed intensified would mean titrating basal insulin upwards, with short-acting mealtime insulin added if necessary

ERG exploratory analyses

ERG revised the company model to create its own base case, using the following new assumptions, including:

- Replaced some company NMA results for effectiveness with trial data
- Patients retained oral treatments when intensifying to insulin
- Added costs of self-monitoring of blood glucose costs (£51/£119 for insulin/intensified), needles (£32) and hypoglycaemia events for insulin
- Used more up to date UKPDS 82 event equations
- Used THIN database for patient characteristics with standard deviations
- Added hypoglycaemia event rates for insulin/intensified
- Used the UTI and GTI cost and QALY decrement estimates from the recent NICE MTA of SGLT2 inhibitors as monotherapy
- Added pioglitazone as a comparator, using BNF costs in base case (£20.99) and eMIMs costs (£225) in a sensitivity analysis. Also included an annual monitoring cost of £72 for BNP monitoring

ERG base case (dapagliflozin vs comparator)

	Incremental cost	Incremental QALY	ICER
DPP4 inhibitors	£651	0.017	£37,997
Empagliflozin 10	-£35	0.004	Dominant
Empagliflozin 25	-£35	0.003	Dominant
Canagliflozin 100	-£124	0.017	Dominant
Canagliflozin 300	£110	0.009	£12,875
Pioglitazone	£4,834	0.009	£558k

ERG scenarios vs DPP4 inhibitors

	Δ Cost	Δ QALY	ICER
Base case	£651	0.017	£37,997
1.Orals discontinued	£143	0.017	£8,351
2.Remove placebo/natural history effect	£650	0.017	£38,147
3.UKPDS 68 event equations	£495	0.02	£25,329
4.No BMI quality of life	£651	0.012	£53,642
5.No patient heterogeneity sampling	£651	0.017	£37,997
6.PSA patient characteristics sampling	£930	0.104	£8,933
7.No discontinuations	£647	0.018	£36,818
8.Not subtracting no complication costs	£639	0.017	£37,294
9.No triple therapy hypoglycaemia	£651	0.01	£68,210
11a.Company NMA: Base case random effects	£677	0.017	£40,735
11b.Company NMA: Base case fixed effects	£677	0.017	£40,792
11c.Company NMA: End point random effects	£681	0.015	£45,499
11d.Company NMA: End point fixed effects	£680	0.015	£44,371
11e.Company NMA: 24 week random effects	£694	0.003	£242k
11f.Company NMA: 24 week fixed effects	£697	0.000	£27mn
Cana: canagliflozin; empa: empagliflozin; k: thousand; mn: million; NMA: network meta-analysis; pio: pioglitazone; PSA: probabilistic sensitivity analysis			

Costs: Dapagliflozin vs DPP4 inhibitors (company scenarios)

Scenario	IHD	MI	CHF	Stroke	Blindness	Nephropathy	Amputation	Hypo-glycaemia	Adverse Events	Treatment	Indirect Costs	Total
Base case	-£6	-£21	-£8	-£18	£0	-£172	-£8	£5	£8	£96	£12	-£112
THIN database	-£5	-£22	-£9	-£26	£1	-£155	-£7	£7	£11	£138	£16	-£51
UKPDS 82	-£6	-£12	-£1	-£14	-£4	£0	-£5	£5	£8	£93	£6	£71
Orals continued	-£6	-£21	-£8	-£18	£0	-£172	-£8	£5	£8	£639	£12	£431
7.5% baseline HbA1c	-£3	-£14	-£5	-£14	£2	-£149	-£5	£27	£17	£377	£7	£240

Costs: Dapagliflozin vs DPP4 inhibitors (ERG scenarios)

	IHD	MI	CHF	Stroke	Blindness	Nephropathy	Amputation	Hypo-glycaemia	Adverse Events	Treatment	Indirect Costs	Total
Base case	-£4	-£2	-£3	-£11	£0	£1	£0	-£15	£21	£658	£7	£651
SA01: Orals discontinued	-£4	-£2	-£3	-£11	£0	£1	£0	-£15	£21	£149	£7	£143
SA02: No placebo effect	-£4	-£2	-£3	-£11	£0	£1	£0	-£15	£21	£657	£7	£651
SA03: UKPDS 68	-£2	-£7	-£3	-£14	£1	-£66	-£1	-£15	£21	£573	£10	£495
SA09: No 3rd line hypo	-£4	-£2	-£3	-£11	£0	£1	£0	-£15	£21	£658	£7	£651
SA11a-f Co NMA scenarios	-£1/ -£7	-£2/ -£12	-£2/ -£3	-£3/ -£26	£0/ -£2	£1/ £2	-£1/ £6	£6	£18	£688/ £678	£3/ £18	£677/ £697

ERG scenarios vs SGLT2 inhibitors and pioglitazone

	Empa 10	Empa 25	Cana 100	Cana 300	Pio
Base case (BC)	DomT	DomT	DomT	£12,875	£558k
Orals discontinued	£2,721	£3,261	DomT	DomT	£133k
Remove placebo effect	DomT	DomT	DomT	DomT	£440k
UKPDS 68 event equations	DomT	DomT	DomT	£8,201	£239k
No BMI quality of life	DomT	DomT	DomT	£11,940	DomD
No patient heterogeneity sampling	DomT	DomT	DomT	£12,875	£558k
PSA characteristics sampling	DomT	DomT	DomT	£3,284	£123k
No discontinuations	£3,729	£6,409	DomT	£27,828	£1.8mn
Not subtracting no complication cost	DomT	DomT	DomT	£12,441	£557k
No triple therapy hypoglycaemia	DomT	DomT	DomT	£80,301	£784k
Pioglitazone £225 per year	n.a.	n.a.	n.a.	n.a.	£270k
NMA: BC random effects	DomD	DomD	DomD	DomD	£501k
NMA: BC fixed effects	DomD	DomD	DomD	DomD	£503k
NMA: End point random effects	DomD	£246SW	DomD	DomD	£454k
NMA: End point fixed effects	DomD	DomD	DomD	DomD	£400k
NMA: 24 week random effects	£18,870	DomT	DomT	DomD	DomD
NMA: 24 week fixed effects	£22,603	DomT	DomT	DomD	DomD

Cana: canagliflozin; DomD: dapagliflozin dominated by comparator; DomT: dapagliflozin dominant; empa: empagliflozin; k: thousand; mn: million; n.a.: not applicable; NMA: network meta-analysis; pio: pioglitazone; PSA: probabilistic sensitivity analysis

Potential equality issues

- No equalities issues identified

PPRS payment mechanism

- Does the company consider the PPRS 2014 Payment Mechanism has an impact on the effective price/cost of dapagliflozin to the NHS?
- Has the Committee heard anything that would change the conclusion in the NICE position statement* on the PPRS?
- “PPRS Payment Mechanism should not be regarded as a relevant consideration in the assessment of cost effectiveness”
- *https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/PPRS%202014%20-%20NICE%20Position%20Statement.pdf

Key issues for consideration (1)

- Dapagliflozin is the only SGLT2 inhibitor not recommended for triple therapy (canagliflozin and empagliflozin are both recommended as triple therapy, but dapagliflozin was not because of a lack of evidence). All SGLT2 inhibitors have the same costs and similar effectiveness. Is there a case for a pragmatic positive recommendation?
- The company used the older UKPDS event equations, rather than using the newer equations which are informed by more follow-up data and have differing rates for certain events. Should the company have used the newer equations?
- For the costs of complications, the company used an older version of UKPDS (65), rather than the updated costs from UKPDS 84. Should the company have used the newer source?

Key issues for consideration (2)

- The costs are affected by whether oral treatments are stopped when is insulin started (as assumed in the company base case) or continued indefinitely (as assumed in the ERG base case). Would people continue on SGTL2 as part of triple therapy once insulin is started? The company argues that few would continue on dapagliflozin after 10 years because of a decline in renal function
- The company assumes that the weight loss for dapagliflozin is maintained for 1 year only, however the ERG suggest this is a pessimistic assumption for dapagliflozin. How long is weight loss likely to be maintained?
- The company and the ERG agree that the QALY benefits of dapagliflozin, driven by differences in the incidence of diabetes related complications and weight loss, are modest, but differ in their estimates of relative costs, the company says that dapagliflozin accrues lower costs, the ERG disagrees. What is the committee's view of the different approaches?