Dapagliflozin STA: BMS-AstraZeneca response to additional questions from the ERG

16 November 2012

Q1. Despite further cross checking of the inputs to the modelling of Table 58 with the clinical effectiveness section of the submission and the literature, the ERG has not been able to source the values for discontinuation rates, hypos, severe hypos, UTI and GI . This is with the exception of those drawn directly from Nauck (Study 4). While the ERG understands that formal clarification has occurred, it would be much appreciated if the manufacturer could outline the sources of these estimates. Table references would be particularly helpful.

Data on discontinuation rates, hypoglycaemia, and the incidence of urinary tract infection (UTI) and genital infection (GI) were extracted within the scope of the systematic literature review and network meta-analyses (NMA) of randomized controlled trials presenting efficacy and safety of anti-diabetic agents in adults with T2DM *(*see attached document *2012 06 29 OXOUT Network meta-analysis of antidiabetic agents metformin add-on 52 week (Dec 6 2011).doc)* . Data on the incidence of UTI and GI were not subject to meta-analysis.

For the add-on to metformin NMA, the extracted safety outcomes of the selected trials are listed in Appendix 8 of the NMA report. The extracted discontinuation rates were listed in Appendix 9 of the NMA report.

For the comparison of dapagliflozin vs DPP4 as add-on to insulin in the cost-effectiveness model, the UTI and GI rate inputs applied for the analyses were sourced from Study 6 (24 week data) for dapagliflozin and from a saxagliptin study by Barnett et al. (2012) for DPP4.

Q2. Please summarise the direct treatment costs for each of the triple therapy comparisons and present the arithmetic underlying these calculations, including the proportions of each therapy that are assumed to underlie these e.g. the balance between the GLP-1s.

Cost-effectiveness analyses were conducted for the following triple therapy comparisons:

	Treatment arm		Control arm		
First line	MET+SU		MET+SU	MET+SU	MET+SU
Second line	MET+SU+Dapagliflozin	**vs**	MET+SU+DPP4	MET+SU+TZD	MET+SU+GLP1
Third line	MET+INS		MET+INS	MET+INS	MET+INS

The treatment costs were based on prices retrieved from the NHS Drug Tariff February 2012, see Table 1. For MET, the drug cost of the cheapest available formulation was applied. For SU, the cost of gliclazide was applied, as gliclazide represents 89% of the SU market in the UK. The cost of sitagliptin, which is 80% of the gliptin market in the UK, was taken for the class of DPP4. For TZD, a weighted average price of pioglitazone was calculated, for a weighted average dose according to the UK market share of pioglitazone doses. The calculated annual treatment costs are presented in Table 2.

For GLP1, a weighted average price of exenatide and liraglutide was calculated according to UK market share, see Table 3. The cost of insulin was applied in the model as a cost per kg body weight per day. The price of the cheapest available human NPH insulin was taken to calculate the drug cost of insulin. The calculation of the daily insulin drug cost per kg body weight is shown Table 4.

The total treatment cost per therapy line in the triple therapy comparisons is presented in Table 5.

It should be noted that all drug costs applied in the triple therapy comparisons are the same as those used in the add-on to metformin analyses, with the addition of the drug cost of GLP1 (which was not a comparator in the add-on to metformin analyses).

Table 1 Drug prices and market shares

Drug class	Drug	Price per pack †	Market share ‡	Remarks
MET	metformin	£ 1.35	–	The cheapest formulation was chosen.
SU	gliclazide	£ 1.07	89%	The price of gliclazide was used, because it is 89% of the SU market in the UK (Source: IMS BPI/HPAI combined data Dec 2011); the 80 mg dose is 83% of glicazide prescriptions (Source IMS Disease Analyzer (Nov 2011 version))
DPP4				
	sitagliptin	£ 33.26	80%	The price of sitagliptin was used, because of 80% marketshare (Source: IMS BPI/HPAI combined data Dec 2011).
	saxagliptin	£ 31.60	10%	
	vildagliptin	£ 31.76	9%	
	linagliptin	£ 33.26	1%	
TZD				
	pioglitazone 15 mg	£ 24.56	34%	The weighted average price was used, because market shares were similar for all three doses. Note: the DDD according to the WHO DDD index 2012 is 30 mg (http://www.whocc.no/atc_ddd_index/).
	pioglitazone 30 mg	£ 34.13	40%	
	pioglitazone 45 mg	£ 37.60	26%	
	pioglitazone weighted average dose (28.8 mg)	£ 31.76	–	
INS	Human NPH insulin	£ 17.50	–	The cheapest available human NPH insulin was chosen: Insuman® Basal (Sanofi-Aventis); 5 × 3-mL cartridge for ClikSTAR® and Autopen® 24.

Abbreviations: DDD, defined daily dose; DPP4, dipeptidyl peptidase 4 inhibitor; INS, insulin; MET, metformin; SGLT2, Sodium-glucose co-transporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

† Prices were retrieved from the NHS Drug Tariff February 2012.

‡ market shares were provided by the manufacturer on March 2nd, 2012.

Table 2 Calculation of annual treatment cost

Drug class	Drug	Price per pack	#Tablets per pack	Dose per tablet (mg)	Daily dose (mg/day)	Annual treatment cost
MET	metformin	£ 1.35	84	500	2000	£ 23.46
SU	gliclazide	£ 1.07	28	80	160	£ 27.90
TZD	pioglitazone	£ 31.76	28	15/30/45	Weighted average (28.8 mg)	£ 414.07
DPP4	sitagliptin	£ 33.26	28	100	100	£ 433.57
SGLT2	dapagliflozin	£ 36.59	28	10	10	£ 476.92

Abbreviations: DPP4, dipeptidyl peptidase 4 inhibitor; MET, metformin; SGLT2, Sodium-glucose co-transporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

Table 3 Treatment cost calculation of GLP1

Product	Price per pack	Rx m/s	Doses per pack	Mcg per dose	DDD (mcg)	Treatment days	Annual cost
Exenatide	£68.24	55%	60	10	20	365	£830.25
Liraglutide	£78.48	45%	2	18000	1200	365	£954.84
Weighted average							**£886.90**

Table 4 Calculation of the daily insulin drug cost per kg body weight

Price per pack	Pens per pack	Dose per pen (IU)	Dose assumption	Daily dose per kg (IU)	Cost/kg/ day
Insulin 3rd line TRIPLE THERAPY ANALYSIS					
£ 17.50	5	300	DDD of 40 IU divided by the mean body weight (88 kg) at baseline of Study 4 †	0.45	£ 0.0053

† Study 4: Study Code D1690C00004; Nauck et al, 2011. DDD = defined daily dose according to the WHO DDD (http://www.whocc.no/atc_ddd_index/).

Table 5 Annual treatment cost in the triple therapy analyses

	Treatment		Annual treatment cost
First line	MET+SU	£ 23.46 + £ 27.90	£ 51.36
Second line	MET+SU+ dapagliflozin	£ 23.46 + £ 27.90 + £ 476.92	£ 528.28
	MET+SU+ DPP4	£ 23.46 + £ 27.90 + £ 433.57	£ 484.93
	MET+SU+ TZD	£ 23.46 + £ 27.90 + £ 414.07	£ 465.43
	MET+SU+ GLP1	£ 23.46 + £ 27.90 + £ 886.90	£ 938.26
Third line	MET+INS	£ 23.46 + £ 0.0053 per kg/day	£ 193.70 for a patient of 88 kg body weight

Abbreviations: DPP4, dipeptidyl peptidase 4 inhibitor; INS, insulin; MET, metformin; SGLT2, Sodium-glucose co-transporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

Q3. Please clarify if the total dose of insulin increases with patient weight in line with the modelled changes in BMI.

The model calculates insulin cost on an 'insulin units per kg' basis. The cost per kg is a user-defined input and the model uses patient weight at each time cycle to calculate insulin cost.

Q4. Within Table 4 of the response to ERG clarification questions please further clarify the calculation of the CV risk factor and the calculation of the BMI risk factor.

The 'CV risk factor' and 'BMI risk factor' are two user defined risk modifiers that enable the model to increase or decrease overall CV risk. The default value for these parameters is 1 (such that CV risk is not modified). These are risk adjustment parameters that can be used to modify CV risk if required (and evidence based). They are not routinely used and their default value in the model is set to 1.

Q5. Within Table 4 of the response to ERG clarification questions the ERG is struggling to locate the MI fatality equation and the Stroke fatality equation within the cited UKPDS 68. Please clarify the source of these, preferably including a table reference. If the MI fatality equation and/or the Stroke fatality equation are transformations of equation(s) within UKPDS 68 it would be much appreciated if the arithmetic underlying this could also be presented.

The model uses a combination of UKPDS 68 and UKPDS 66 by default to calculate MI and stroke fatality. The specific MI and stroke fatality equations shown in Table 4 should have been referenced to:

Stevens RJ et al. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. Diabetes Care. 2004 Jan;27(1):201-7

These are used by default in the model and provide estimates of the probability that an MI or stroke event is fatal. The event fatality and diabetes mortality equations from UKPDS68 are used in the model to calculate non-MI and non-stroke event related mortality and subsequent diabetes related mortality.

Q6. Within Table 4 of the response to ERG clarification questions the event equation for MI and the event equation for Stroke appear to include both non-fatal and fatal events, based upon the text of UKPDS 68. For mortality associated with events equation 8 of the UKPDS 68 relates to event incidences of MI, CHF, stroke, amputation and renal failure, with equation 9 relating to having had a history of any of these events: i.e. they both include MI and Stroke. UKPDS 68 equation 8 is implemented in the "Event Fatality" equation of table 4 of the response to ERG clarification questions, but there is no reference to UKPDS equation 9 in table 4. Please clarify how the following three fatality event equations of table 4 of the response to ERG clarification questions are related, with particular reference to UKPDS 68:

- **Event fatality**
- **MI fatality**
- **Stroke fatality**

As per response to Q5 above, MI and stroke events invoke the UKPDS 66 event fatality equations and UKPDS 68 diabetes mortality equation in subsequent years. All other potentially fatal diabetes specific events invoke the UKPDS 68 event fatality and diabetes mortality equations.

Q7. Related to Table 4 of the response to ERG clarification questions please further clarify if the event equation 9 (diabetes mortality) and/or the event equation 10 (general mortality) from UKPDS 68 are applied within the CARDIFF/DCEM model. If they are, are they additional mortality risks over and above those specified in table 4 of the response to ERG clarification questions; i.e. in addition to Event fatality, MI fatality and Stroke fatality.

The model does not use the general mortality equation from UKPDS 68. The model uses age and gender specific life tables from which the risk of diabetes specific mortality is first subtracted to avoid double counting. This risk adjustment is performed at each time cycle.

Q8. Please clarify if the event rates are discounted: e.g. those of table 73 of the submission.

The event rates are not discounted. Only costs, life years and quality adjusted life years are discounted in the model.

Q9. Please clarify if the times on treatment are discounted: e.g. those of table 74 of the submission.

Time on treatment is not discounted in the model.

Q10. Please clarify if the utility decrements in T2 Events worksheet AZ66:BB68 are discounted and if subtracted from the total in AR32 would result in the total QALYs if there were no utility decrements from events, weight and hypos.

The utility values presented in T2 Events worksheet AZ66:BB68 are the per-patient cumulative sum (over simulated time-horizon) of event related, hypo related and weight related dis-utility. These calculations are not intended to be used to compare the difference in total QALYs between the two modelled treatment arms, as they do not collect all disutilities calculated by the model (for example they do not include treatment related disutility). Their inclusion is designed to illustrate how much weight; hypoglycaemia and vascular complications contribute to the average per-patient QALY changes.