MSD Comments: Consultation on ACD – Dapagliflozin in combination therapy for treating type 2 diabetes

General comment on the ACD:

As acknowledged by the ERG and the DSU, there are significant concerns over the reproducibility of the economic model. It appears the that the model submitted does not comply with the requirements of the NICE Guide to Methods of Technology Appraisals[1], which states that the model should follow accepted guidelines, and full documentation and justification of structural assumptions and data inputs should be provided. Until these concerns are resolved satisfactorily and the manufacturer can provide a robust model in which both the ERG and DSU have confidence, we feel it would be inappropriate for a positive recommendation to be made on the use of dapagliflozin.

Comments by section number of the ACD

- **Section 3.15 - Dapagliflozin in triple therapy**

The ACD confirms that the assessment of clinical effectiveness of dapagliflozin compared with DDP-4 inhibitors, GLP-1 analogues and thiazolidinediones was based on indirect evidence. The manufacturer has referred to a literature review concerning add-on therapy to metformin and sulfonylurea produced in 2009 from the Canadian drugs agency. However new data is available since then including studies of the newer DPP-4 inhibitors (linagliptin and saxagliptin). This newer data has not been captured in the analysis as the manufacturers did not conduct an up-to-date systematic review of triple therapy for people with type 2 diabetes inadequately controlled with metformin and sulfonylurea. Consequently we do not consider that any robust conclusions can be drawn from the indirect evidence presented in the submission for triple therapy.

- **3.16 Cost effectiveness**

The economic model should be updated to reflect the safety issues associated with pioglitazone, as acknowledged in section 4.3 of the ACD. The incremental dapagliflozin associated renal monitoring cost (as required in line with the marketing authorisation for Dapagliflozin) should also be incorporated into the economic model.

- **Sections 3.21, 3.36 and 4.18 – HbA_{1c} thresholds applied in the model**

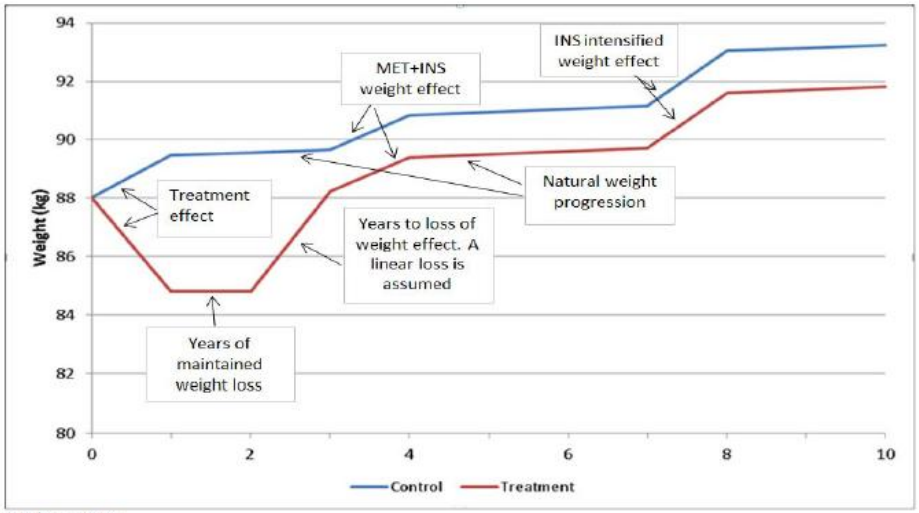
MSD agrees with the concerns raised by the ERG and the NICE Appraisal Committee regarding the inconsistencies in the HBA_{1c} thresholds applied in the manufacturer's cost-effectiveness model, which were not consistent with the NICE Clinical Guideline for Type 2 Diabetes (NICE CG87)[2]. The base-case analyses should use HBA_{1c} thresholds that are consistent with the NICE Clinical Guidelines for Type 2 Diabetes.

- **Section 3.22 – modelling patient weight over time**

The manufacturers have stated that in their modelling the weight reduction for dapagliflozin was assumed to be maintained for two years, based on 2-year extension data. This assumption raises two concerns. Firstly, extension data is self-selecting in nature and therefore, making any assumptions about the potential of dapagliflozin to provide sustained weight loss benefit versus the comparators based on this is highly speculative, at best.

Secondly, the manufacturers appear to have modelled that patients treated on dapagliflozin have a lower weight than patients treated on the comparators for the whole time horizon of the model (i.e. 40 years), as highlighted below by Figure 27 from the manufacturer's submission[3]. Figure 27 from the manufacturer's submission, shows that the weight of patients on both treatments converge to the original weight of the patient at treatment initiation between year 2 and 3 (as the manufacturer state). However, after 3 years, Figure 27 shows that the patients on treatment (i.e. dapagliflozin) continue to have a lower weight compared to the patients on the 'control' (i.e. comparator). This assumption is not based on any evidence.

Figure 27. Illustration of dynamic body weight profile implemented in the model



x axis = years

Additionally, the weight loss due to dapagliflozin is not uniform for all T2DM patients, and therefore weight loss has to be adjusted for a patient's baseline body weight and/or their BMI. The weight loss assumption for dapagliflozin is the key driver of the cost-effective model. The approach used by the manufacturer brings into question the reliability and robustness of their cost-effectiveness results. Amendments to these assumptions regarding weight change after 52 weeks do not appear to have been requested as part of the Committee's recommendation for further analyses from the manufacturer.

- **<u>Section 3.25 – ERG's estimated cost of a severe hypoglycaemic event</u>**

The ERG estimated the direct costs of a severe hypoglycaemic event from the Hammer et al. study to be £320 compared to the manufacturer's estimate of £390 (section 5.3.2, ERG Report). MSD believes that the manufacturer has correctly calculated the direct cost of a severe hypoglycaemic event as £390.

The total UK direct costs for patients with type 2 diabetes reported in Table 5 of Hammer et al. (2009)[4] for three groups of patients that were categorised based on the way their hypoglycaemic event was managed were £33, £231 and £862 (in 2007 prices). Hammer et al. reported that the prevalence of the three treatment groups in the general population was 47.4%, 18.4% and 34.2%, respectively (based on Table 2 & 7 in the Hammer et al. publication). By applying these weightings, the average direct cost of a hypoglycaemic event is £353 in 2007 prices. Inflating this price (using the Hospital and Community Health Services Pay and Prices Index[5]) by 10.48% to 2011 prices equates to £390, as calculated by the manufacturer.

In the ERG's estimated cost of £320, they based their weightings on the percentage of participants that were recruited in each treatment group in the study. As stated by the authors of the Hammer et al., study recruitment used a "non-random selection process". Therefore, it is more appropriate to apply the prevalence of the three treatment groups in the general population reported by Hammer et al. (as the manufacturer did) rather than the weightings of study participants, which are not representative of the general population.

- **Section 3.25 – costs of managing urinary tract infections (UTIs) and genital infections**

The manufacturer assumed that the cost of treating a UTI or genital infection is only associated with the cost of one GP visit (£36). MSD believes this is an underestimate of the NHS resource and cost associated with treating UTIs and genital infections.

UTIs and genital infections increase the risk of patients requiring GP visits, prescriptions and potentially hospital visits. Health Protection Agency guidance recommends treatment with antibiotics in severe cases or if the patient has ≥ 3 symptoms, and in mild cases depending on the results of the dipstick test and the presence of cloudy urine. It is therefore likely that additional drug therapies would need to be considered in some cases if a patient were to develop a UTI or genital infection as an adverse reaction to dapagliflozin therapy[6].

- **Section 3.32 – ERG comments on scope of appraisal**

The ACD states:

"*Overall, the ERG considered that DPP-4 inhibitors are the key comparators for dapagliflozin in both the dual therapy and triple therapy settings*."

This statement is inconsistent with the algorithms for dual therapy in the NICE Clinical Guideline 87 for Type 2 Diabetes[2]. For add-on to metformin, sulfonylureas, DPP-4 inhibitors and thiazolidinediones are recommended in the NICE Guidelines. While the use of pioglitazone (the only thiazolidinedione available in the UK) is in decline because of concerns about safety, sulfonylureas are commonly used. As such, both DPP-4 inhibitors and sulfonylureas are both key comparators for the dual therapy setting.

- **Section 3.40 – Price of DPP-4 inhibitors**

The revised annual cost of DPP-4 inhibitors of £450.51 estimated by the ERG and reported in the ACD is not appropriate. The appropriate cost for DPP-4 inhibitors (based on sitagliptin) to use in this analysis is £433.57, which is the same as that used by the manufacturer.

The most commonly used DPP-4 inhibitor in England is sitagliptin 100mg (Prescription Cost Analysis Data, 2011[7]), which has an annual cost of £433.57 (Drug Tariff, February 2013[8]). Regarding the cost of DPP-4 inhibitors, the dapagliflozin ERG report states the following:

"Note that sitagliptin in combination with a metformin total daily dose of 1g is available at an annual cost of £450.51"

There are two issues if this price is used in the analyses for DPP-4 inhibitors:

- firstly, sitagliptin 100mg rather than the sitagliptin/metformin combination product accounts for the majority of sitagliptin and DPP-4 inhibitor usage (Table 1)[7]. Therefore, the cost of DPP-4 inhibitors should either be based on the cost of the most commonly prescribed DPP-4 inhibitor (sitagliptin 100mg, £433.57 per patient/per year) or on a weighted average cost taking into account the level of usage of each DPP-4 inhibitor and DPP-4 inhibitor/metformin combination product;

Table 1: Number of prescriptions for sitagliptin and combination products in England, 2011[7]

Drug & Dose	Number of prescriptions in England, 2011	% of DPP-4 inhibitor prescriptions, 2011
Sitagliptin 100mg	1,155,340	77.8%
Saxagliptin 5mg	98,290	6.6%
Vildagliptin 50mg	81,181	5.5%
Vildagliptin 50mg/metformin 1g	64,467	4.3%
Sitagliptin 50mg/metformin 1g	51,221	3.5%
Vildagliptin 50mg/metformin 850mg	20,205	1.4%
Saxagliptin 2.5mg	12,090	0.8%
Linagliptin 5mg	1,864	0.1%

- secondly, the cost of metformin is inputted separately in the cost-effectiveness analyses. If the cost for this combination product of sitagliptin and metformin (£450.51) is applied for DPP-4 inhibitors, it is necessary to remove the cost of metformin (£23.46, Table 62, Dapagliflozin manufacturer's submission[3]) to avoid double counting the costs associated with metformin. In the ERG's re-analyses, it is not clear as to whether this was accounted for.

- **Section 3.40 – Price of pioglitazone**

As noted by the ERG, the price of pioglitazone has fallen compared with that reported in the manufacturer's submission for dapagliflozin (which was based on the February 2012 Drug Tariff). This is because pioglitazone was added to Category M in the Drug Tariff in April 2012. While the ERG noted that the Drug Tariff price of pioglitazone was "£139.16" in the November 2012 Drug tariff (Dapagliflozin ERG Report), the price has fallen significantly since then.

Table 2 below summarises the weighted average cost of pioglitazone compared to the Drug tariff in February 2012 (the source used by the manufacturer), November 2012 (the source used by the ERG) and February 2013 (the latest price available), based on the weightings that were reported in the manufacturer's submission. Between November 2012 and February 2013, the weight average cost of pioglitazone has fallen from £112.18 to £69.06 (a 38.4% price reduction).

Table 2: Weight average annual cost of pioglitazone, based on Drug Tariff prices between February 2012 and February 2013

Drug & dose	Weighting reported by manufacturer[7]	Drug Tariff Price (28 tablet pack)		
		February 2012[9]	November 2012[10]	February 2013[8]

Pioglitazone 15mg	34%	£24.56	£6.61	£4.28
Pioglitazone 30mg	40%	£34.13	£8.96	£5.31
Pioglitazone 45mg	26%	£37.60	£10.67	£6.61
Weighted average cost of pioglitazone		**£414.25**	**£112.18**	**£69.06**

- **Section 4.2 – clinical effectiveness of dapagliflozin in triple therapy**

MSD do not consider that sufficiently robust evidence has been submitted by the manufacturers to allow a recommendation to be made for use of dapagliflozin as part of a triple therapy regime.

- **Section 4.9, 4.11 and 4.12 – network meta-analysis**

The network meta-analyses submitted by the manufacturer provided most of the clinical effectiveness data for the comparison of dapagliflozin and other anti-diabetic therapies. However we are concerned by the level of uncertainty surrounding the validity of the results of the network meta-analyses. This therefore makes any results presented questionable, and until the issues with the programme code which has been used to run the network meta-analyses are resolved, we believe that the results presented cannot be considered as robust. Consequently the weight loss benefit claimed to be shown by dapagliflozin is yet to be proven conclusively.

- **Section 4.10 – comparative clinical-effectiveness data at 24-weeks and 52-weeks**

The ACD states:

"*The Committee also heard from the manufacturers that 2-year follow-up data were available for the clinical trials of dapagliflozin but that, because most of the trials of other antidiabetic drug therapies were of 24-week duration, it was necessary that the clinical-effectiveness data used in the cost-effectiveness analysis were based on the results of the clinical trials and network meta-analyses at 24 weeks.*"

There is clinical-effectiveness data available from the manufacturer's network meta-analysis at 52-weeks for the add-on to metformin analysis for the following outcomes:

- HbA1c
- Weight change
- Hypoglycaemic event

Given the long-term time horizon of the model, the NICE Appraisal Committee need to consider the cost-effectiveness results based on the 52-week data for these endpoints (presented as a scenario analysis by the manufacturer) in addition to the base case analysis using 24-week data, as part of their deliberations.

- **Section 4.13 – Adverse events**

The ACD confirms that the Committee has heard from patient groups that adverse events are a concern for patients with type 2 diabetes if they result in the need for additional drug therapies. The most common adverse events for dapagliflozin were urinary tract infections (UTIs) and genital infections.

UTIs and genital infections increase the risk of patients requiring GP visits, prescriptions and potentially hospital visits. Health Protection Agency guidance recommends treatment with antibiotics in severe cases or if the patient has ≥ 3 symptoms, and in mild cases depending on the results of a dipstick test and the presence of cloudy urine. It is therefore likely that additional drug therapies would need to be considered in some cases if a patient were to develop a UTI or genital infection as an adverse reaction to dapagliflozin therapy[6].

- **Section 4.17 – Interpretation of cost-effectiveness results for add-on to metformin (dual therapy)**

The manufacturer sourced the clinical effectiveness data for the metformin add-on analyses from different sources. The Committee has acknowledged that it "*would have been preferable to use clinical-effectiveness data from the same source for all comparators*". However, MSD is concerned about the impact this has the interpretation of the cost-effectiveness results for the add-on to metformin scenario.

For the 'dual therapy ' add-on to metformin analyses, it is not appropriate to directly compare the incremental cost-effectiveness ratio (ICER) obtained from the dapagliflozin versus SU analysis to the ICERs obtained from the dapagliflozin, DPP-4 inhibitors, glitazones analysis because the clinical-effectiveness estimates have been derived from different sources. As a consequence, the cost-effectiveness results for the add-on to metformin cannot be directly compared and incrementally analysed to identify situations of simple or extended dominance across all the comparators. The NICE Guide to Methods of Technology Appraisals states the requirement to assess dominance in cost-effectiveness analyses:

"*Standard decision rules should be followed when combining costs and QALYs. These should reflect any situation in which dominance or extended dominance exists.*"[1]

As such, the approach used by the manufacturer poses further uncertainty in the cost-effectiveness results for the metformin add-on analysis.

References

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