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

**Comments by section number of the ACD**

- **Section 2.5 – the expected annual cost of empagliflozin 10mg and 25mg**

The expected annual cost of empagliflozin 10mg and 25mg of £470.30 reported in the ACD appear to be incorrectly calculated, given the cost per 28-tablet pack is £36.59. The annual expected cost of empagliflozin 10mg and 25mg is £476.98 (assuming that there are 365 days per year).

- **Section 3.12 to 3.15 – General comment on the manufacturer's network meta-analysis**

Sections 3.12 to 3.15 describe and present the results from the manufacturer's network meta-analyses and include interpretations of the results. The results from the network meta-analysis should be presented with mean differences with associated 95% credible intervals between all interventions – this has not been done in section 3.15 of the ACD. Statements using "generally comparable", "more likely to result in reductions in body weight and blood pressure" and "showed better reduction in HbA1c levels" are subjective and meaningless. Please present the data using mean differences with associated 95% credible intervals for every drug and dose included in each network meta-analysis for each endpoint in each indication.

- **Section 3.15 – network meta-analysis for urinary tract and genital infections**

In section 3.15 there is a statement "The incidence of urinary tract and genital tract infections was comparable between empagliflozin and other treatments." Using indirect evidence to compare the incidence of adverse events of treatments is subjective. In the manufacturers submission, page 177, the lack of evidence to infer differences between some comparisons (e.g. between drugs within the same SGLT2 class), and the extremely wide 95% credible intervals indicates there is a great deal of uncertainty in comparing adverse events, and in particular the incidence of urinary tract infections. We believe any results that lead to this degree of uncertainty in the network meta-analysis should be removed from the ACD with a focus on direct evidence.

- **Section 3.28 – modelling urinary tract and genital infections**

In this section, it is reported that the manufacturer assumed that "urinary tract infections and genital infections were assumed to happen only in the first cycle after starting treatment". A fixed cycle length of 6 months was used in the manufacturer's cost-effectiveness model. However, as reported earlier, a number of the Phase III randomised clinical trials for empagliflozin had a duration over 6 months, and in some cases, up to 2 years. As such, there is safety data related to urinary tract infections and genital infections for beyond 6 months, and the modelling should reflect the longer-term rates of urinary tract and genital infection rates, along with recurrence rates observed from the full clinical data available.