MSD Response

26th January 2016

MSD welcomes the opportunity to comment on the ACD for "Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes".

Incomplete information on adverse reactions

MSD believes that the ACD provides incomplete information of adverse reactions of SGLT2-i. More specifically:

- On page 6, the ACD discusses cangliflozin's adverse reactions as follows: "The summary of product characteristics lists the following adverse reactions for canagliflozin as the most commonly reported: vulvovaginal candidiasis, urinary tract infection, and polyuria. For full details of adverse reactions and contraindications, see the summary of product characteristics."

MSD requests that all common adverse reactions are listed in this section. Even if the reader is referred to the summary of product characteristics, the way this sentence is written implies that the most commonly reported adverse reactions of cangliflozin are only vulvovaginal candidiasis, urinary tract infection, and polyuria. All most commonly reported adverse reactions should be listed in the ACD – balanitis, dyslipidaemia, haematocrit increase, constipation, thirst and nausea should be also reported here.

- On page 6, the ACD discusses dapagliflozin's adverse reactions as follows: "The summary of product characteristics lists the following adverse reactions for dapagliflozin: urinary tract and genital infection, back pain, dysuria, polyuria, dyslipidaemia and elevated haematocrit."

As above, MSD requests that all common adverse reactions are listed in this section - vulvovaginitis, balanitis, dizziness and creatinine renal clearance decreased should be also reported here.

- On page 7, the ACD discusses empagliflozin's adverse reactions as follows: "The summary of product characteristics includes the following adverse reactions for empagliflozin: urinary tract infection and polyuria."

As above, MSD requests that all common adverse reactions are listed in this section - vulvovaginitis, balanitis and pruritus should be also reported here.

- On page 9, the ACD only discusses UTIs and GTIs, but there are no discussion on the risk of cardiovascular events, bone health and diabetic ketoacidosis.

MSD believes that all adverse events and warnings associated with SGLT2-i should be reported here. The Assessment Group (AG) dedicated a whole section to diabetic ketoacidosis, cardiovascular events and bone health, and these should be mentioned in the ACD. Moreover, NICE specifically mentions the risk of diabetic ketoacidosis with SGLT2-i in the new NG28 and the ACD should be consistent with the guideline.

Misleading information on adverse reactions

On page 9, the ACD states: "No evidence of a dose-response relationship was found with any treatment". MSD believes that this statement is not true for canagliflozin. The 300mg dose of canagliflozin is associated with higher rates of adverse events, as reported in Schernthaner et al. 2013[1]. More specifically, the study found that "higher incidence of genital mycotic infections and osmotic diuresis-related adverse events were observed with canagliflozin, which led to one discontinuation."

Superior efficacy of SGLT2-i over the DPP4-i

The claims of superior efficacy of the SGLT2-i over the DPP4-i in the ACD are quite difficult to interpret. More specifically:

- On page 8, the ACD states: ***"The reductions for empagliflozin were also greater than those for sitagliptin (statistical significance was not presented)"***

The ACD here is referring to the study of Roden et al. 2013, used by the AG. As we have already stated in our consultation on the Assessment Report (AR), MSD is concerned about the robustness of the conclusions of the AG regarding empagliflozin vs sitagliptin, because (a) the study did not use sitagliptin in line with its UK license (restricted monotherapy in patients who are not controlled or who cannot tolerate metformin); (b) the study applied open-label regime in its study design – this is inappropriate for the purpose of comparison and could bias the results. The authors of the study themselves state that "*The comparisons between empagliflozin and sitagliptin were only exploratory and therefore no firm conclusions to be made about the comparative efficacy of these drugs*" and (c) the study duration of 24 weeks is relatively short - MSD believes that firm conclusions cannot be drawn from this length of study and that this does not allow the durability of the study drugs to be fully assessed. MSD believes that the only appropriate monotherapy study for sitagliptin is Aschner 2010 where the baseline was much lower (7.2%) and therefore the reduction observed in HbA1c was only 0.43%. Another appropriate study is Aschner 2006, which the Assessment Group rightly included in the NMA.

- On page 11, the document states: ***"Compared with DPP-4 inhibitors, it resulted in a greater reduction in HbA1c, weight and systolic blood pressure (all results statistically significant, other than compared with sitagliptin for HbA1c, where there was no difference)"***

The ACD here is referring to the NMA that Janssen provided to NICE for their submission. MSD believes that more caution should be applied with the wording of this statement, as none of the sitagliptin studies used in the NMA compared canagliflozin directly with sitagliptin. MSD would welcome the removal of the statement.

- On p. 13 the document states: ***"Compared with sitagliptin, SGLT-2 inhibitors were more effective for HbA1c (in some instances this reached statistical significance)"***

This statement refers to the NMA conducted by the AG. The studies for sitagliptin were Aschner 2006, Roden 2013 and Stenlof 2013[2]. As mentioned above, MSD believes that Aschner 2006 is an appropriate monotherapy study, but Roden 2013 is not. Regarding Stenlof 2013, the study did not use sitagliptin, but only considered it in extension in a 52-week study (therefore not meeting the inclusion criteria). Moreover, patients were switched to sitagliptin from placebo and sitagliptin was added in the study only for safety purposes. Therefore, MSD believes that results from this study should not be taken into account.

Additionally, MSD would like to stress that SGLT2-i studies are generally performed in patients with high baseline HbA1c and therefore the drop is larger (as with any other glucose-lowering medication).

References

1. Schernthaner G et al., Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea – A 52-week randomized trial. Diabetes Care. 2013(36):2508-2515.
2. Stenlof K et al. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Current Medical Research & Opinion. 2014;30(2):163-75.