National Institute for Health and Care Excellence

Multiple Technology Appraisal (STA/MTA)

Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes

Section	Consultees	Comments	Action
Background information	Boehringer Ingelheim	None	Comments noted. No action required.
	Janssen	Janssen accepts the background information is complete and accurate. Janssen noticed one typological mistake: “A rapid therapeutic response is required because of hypoglycaemic symptoms” should read “a rapid therapeutic response is required because of hyperglycaemic symptoms”.	Comments noted. The background section has been updated.
	AstraZeneca	No comment	No action required.
	Association of British Clinical Diabetologists/ Royal College of Physicians	Background information is complete and accurate	Comments noted. No action required.

Section	Consultees	Comments	Action
	Merck Sharp and Dohme	Regarding the need for this MTA: It is questionable whether there is value to the NHS in pursuing this MTA, as metformin and sulfonylureas account for >96% of the monotherapy market in type 2 diabetes. Additionally, at a time of increasing pressure on NICE, the continuation of this MTA does not appear to be an appropriate use of NICE resources. Timing of CG87 update: CG87 is currently under review with publication due in August 2015, however, the publication of the draft clinical guideline is 10 December 2014. If this MTA is to go ahead we believe it would be appropriate to wait for the advice from CG87 update in order to ensure that the current guidance for monotherapy is followed and an accurate PICO is used during MTA development.	Comments noted. Scoping workshop attendees noted that following referral, the interventions had only been partially appraised (as combination therapy). Therefore the monotherapy part of the referral still required appraisal. Scoping workshop attendees agreed that the proportion of the type 2 diabetes population that would be affected by this appraisal was small. However, given this is a small proportion of a large population this would be an important appraisal for a significant amount of people. NICE delayed the appraisal so the scope could take into account any updated draft recommendations from the review of the diabetes clinical guideline.

Section	Consultees	Comments	Action
The technology/ intervention	Boehringer Ingelheim	The following section *Through this mechanism, canagliflozin, dapagliflozin and empagliflozin may help control glycaemia independently of insulin pathways.* Insulin pathways could be changed to beta cell function Also the highlighted phrase should be added Empagliflozin has a UK marketing authorisation for the "treatment of type 2 diabetes mellitus *in adult patients* to improve glycaemic control in adults as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance".	Comments noted. This section of the scope is intended to provide a brief overview of the technology.
	Janssen	Yes. In addition to the scope text, by inhibiting sodium glucose co-transporter 2 (SGLT2), canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG). This in turn increases urinary glucose excretion (UGE), lowering elevated plasma glucose concentrations in an insulin-independent manner, in patients with type 2 diabetes mellitus (T2DM). The increased UGE with SGLT2 inhibition also translates to an osmotic diuresis, with the diuretic effect leading to a reduction in systolic blood pressure (SBP); the increase in UGE results in a loss of calories and therefore a reduction in body weight, as has been demonstrated in studies of patients with T2DM. In phase 3 studies, pre-meal administration of canagliflozin 300 mg provided a greater reduction in postprandial glucose excursion than observed with the 100 mg dose. This effect at the 300 mg dose of canagliflozin may, in part, be due to local inhibition of intestinal SGLT1 (an important intestinal glucose transporter) related to transient high concentrations of canagliflozin in the intestinal lumen prior to medicinal product absorption (canagliflozin is a low potency inhibitor of the SGLT1 transporter). Studies have shown no glucose malabsorption with	Comments noted. The innovative nature of the interventions will be considered as part of the full appraisal.

Section	Consultees	Comments	Action
		canagliflozin. Furthermore, a review of the summary of product characteristics demonstrated a greater urinary glucose excretion with canagliflozin compared to dapagliflozin 10 mg and empagliflozin (77 to 119 g/day, 70 g/day, and 78 g/day, respectively). Canagliflozin unlike dapagliflozin is also indicated for use in patients with renal impairment and taking pioglitazone. [reference: https://www.medicines.org.uk/emc/medicine/28401; https://www.medicines.org.uk/emc/medicine/27188; https://www.medicines.org.uk/emc/medicine/28974] In the canagliflozin development program, canagliflozin 300 mg consistently provided greater efficacy than canagliflozin 100 mg. Based on results from mechanism of action studies performed with canagliflozin, the greater efficacy with canagliflozin 300 mg compared to canagliflozin 100 mg was attributed to a combination of two different pharmacodynamic effects: (1) canagliflozin 300 mg provides greater suppression of RTG than canagliflozin 100 mg, particularly in the overnight period, leading to greater UGE and (2) canagliflozin 300 mg has an additional (non-UGE related) effect to reduce postprandial glucose excursions in the first meal after dosing that is most likely due to transient inhibition of intestinal SGLT1; this effect is not observed with canagliflozin 100 mg. Based on cross-study comparisons between canagliflozin and dapaglilfozin studies, it was predicted that canagliflozin 300 mg would also have greater pharmacodynamic effects on RT¬G, UGE, and postprandial glucose excursions compared to dapagliflozin 10 mg; a head-to-head study (DIA1056, recently completed but not yet published) was performed to formally test this hypothesis. [reference: http://clinicaltrial.gov/ct2/show/NCT01877889?term=DIA1056&rank=1]	
	AstraZeneca	Yes	Comments noted. No action required.
	Merck Sharp and Dohme	No comment	No action required.

Section	Consultees	Comments	Action
Population	Boehringer Ingelheim	None	Comments noted. No action required.
	AstraZeneca	In order to reflect current clinical practice whereby most patients will receive metformin or a sulphonylurea as their first line oral anti-diabetic drug we recommend that the population is amended to: *"People with type 2 diabetes for whom the use of both metformin and a sulphonylurea is inappropriate (i.e. these treatments are not tolerated or contraindicated or cases where the use of a sulphonylurea is inappropriate due to weight gain or an increased risk of hypoglycaemia)"* The SGLT-2s are only likely to be used as monotherapy in this patient group for whom the use of both metformin and a sulphonylurea is inappropriate.	Comments noted. NICE will appraise the technologies in line with their marketing authorisations.
	Merck Sharp and Dohme	Patients with renal impairment are a critical subgroup of patients. These patients will be contraindicated or intolerant to metformin or an SU, and dependant on degree of renal impairment intolerant/contraindicated to an SGLT-2 also.	Scoping workshop attendees agreed that the wording of the licences meant that anyone using the technologies should have relatively well maintained renal function. Therefore they agreed not to add those with renal impairment as a subgroup.

Section	Consultees	Comments	Action
Comparators	Boehringer Ingelheim	DPP-4i should be added since it is currently used as an alternative to SUs, although not in large numbers.	Comments noted. Scoping workshop attendees agreed that DPP-4 inhibitors and pioglitazone are used in clinical practice and therefore should be added as comparators. In addition, the updated draft clinical guideline for type 2 diabetes includes repaglinide, therefore this has also been added as a comparator.
	Janssen	It is proposed that the treatment comparators for this appraisal are all SGLT-2 inhibitors licensed to date and sulphonylurea (SU). Janssen believes these comparators to be the only significant comparators of interest. Those AHAs considered to be established and relevant to today in clinical practice for monotherapy treatment of T2DM are metformin and SU. NICE clinical guidelines (CG) also propose the use acarbose if a person is unable to use other oral AHAs, however, market share analyses demonstrate that in practice use has reduced significantly over the years and current use in the NHS is negligible. A similar pattern of market share was also identified for rapid acting insulin secretagogues. Therefore, Janssen does not believe that these AHAs should be considered as part of this appraisal. In addition, Janssen do not believe that dipeptidyl peptidase (DPP) -4 inhibitors should be included as comparators in this appraisal. DPP-4 inhibitors are well established in the market in accordance with current recommendation of use as add-on therapy. There has been no published suggestion of clinical desire to review this class of AHAs for use as monotherapy. Moreover, data have not proven significant clinical benefit of treating with	Comments noted. Scoping workshop attendees agreed that DPP-4 inhibitors and pioglitazone are used in clinical practice and therefore should be added as comparators. In addition, the updated draft clinical guideline for type 2 diabetes includes repaglinide, therefore this has also been added as a comparator.

Section	Consultees	Comments	Action
		sitagliptin above and beyond current standard of care. Conversely, SGLT2 inhibitors not only have been shown to significantly reduce HbA1c levels, trials also have proven clinically meaningful reductions in SBP and body weight when treating as monotherapy. [reference: https://www.medicines.org.uk/emc/medicine/19609; Stenlöf et al (2014) CMRO. 30(2):163-175; Stenlöf et al (2013) Diab Obesity & Metabol. 15:372-382; Roden et al (2013) Lancet. 1:208-219; Ferrannini et al (2010) Diabetes Care. 33(10):2217-2224] Finally, only 3% market share has been identified for the use of DPP-4 inhibitors in monotherapy management of T2DM. [reference: Cegedim Strategic Data. April 2014]	
	AstraZeneca	Taking account of the patient population specified above the most appropriate comparators are the DPP-4 inhibitors. In response to the specific consultation question on other possible comparators we would highlight that insulin secretagogues and/or acarbose are rarely used in clinical practice and as a consequence are not appropriate comparators.	Comments noted. Scoping workshop attendees agreed that DPP-4 inhibitors and pioglitazone are used in clinical practice and therefore should be added as comparators. In addition, the updated draft clinical guideline for type 2 diabetes includes repaglinide, therefore this has also been added as a comparator.

Section	Consultees	Comments	Action
	Association of British Clinical Diabetologists/ Royal College of Physicians	The use of a sulphonyl urea as the comparitor agent is logical as this would traditionally be the next agent added. The question arises as to whether a DDP-IV inhibitor should be included in the analysis, even if not as a comparitor. If an individual proves intolerant of metformin, alternatives to an SU might include a DDP-IV inhibitor or an SGLT-2 inhibitor where there is a risk of hypoglycaemia or weight gain is a major factor. An analysis of both agents as monotherapy would be useful.	Comments noted. Scoping workshop attendees agreed that DPP-4 inhibitors and pioglitazone are used in clinical practice and therefore should be added as comparators. In addition, the updated draft clinical guideline for type 2 diabetes includes repaglinide, therefore this has also been added as a comparator.
	Merck Sharp and Dohme	In the NHS, standard clinical practice for monotherapy is as follows: metformin is first line, followed by a sulfonylurea when metformin is not tolerated or is contraindicated, and these two groups account for >96% of patients in monotherapy. Post this glitazones (TZDs), DPP-4 inhibitors and GLP-1 inhibitors are used to varying degrees in monotherapy. Careful consideration should be given whether to include these additional therapies as comparators.	Comments noted. Scoping workshop attendees agreed that DPP-4 inhibitors and pioglitazone are used in clinical practice and therefore should be added as comparators. In addition, the updated draft clinical guideline for type 2 diabetes includes repaglinide, therefore this has also been added as a comparator.
Outcomes	Boehringer Ingelheim	None	Comments noted. No action required.
	Janssen	Janssen believes the outcome measures are appropriate.	Comments noted. No action required.

Section	Consultees	Comments	Action
	AstraZeneca	We recommend that changes in total body weight and systolic blood pressure are also included as additional outcomes.	Comments noted. Scoping workshop attendees agreed that the most important outcomes to specify were urinary tract infections, genital infections and malignancies. Other outcomes not specified in the scope may be considered as part of the full appraisal.
	Association of British Clinical Diabetologists/ Royal College of Physicians	Data on long term outcomes will not currently be available. The main outcomes will be glycaemic control and quality of life due to side effects of treatment. As monotherapy, it will be important to examine glycaemic outcomes in individuals with only moderately raised blood glucose levels as the SGLT-2 inhibitors may not be maximally effective in the group with only marginally elevated HbA1c levels.	Comments noted. Scoping workshop attendees agreed that the most important outcomes to specify were urinary tract infections, genital infections and malignancies. Other outcomes not specified in the scope may be considered as part of the full appraisal.
	Merck Sharp and Dohme	Please include the following with adverse effects of treatment: gastrointestinal, UTI's, increase in LDL-c, blood pressure, renal function, malignancy.	Comments noted. Scoping workshop attendees agreed that the most important outcomes to specify were urinary tract infections, genital infections and malignancies. Other outcomes not specified in the scope may be considered as part of the full appraisal.
Economic analysis	Boehringer Ingelheim	None	Comments noted. No action required.

Section	Consultees	Comments	Action
	Janssen	No comment	No action required.
	AstraZeneca	No comment	No action required.
	Merck Sharp and Dohme	No comment	No action required.
Equality and Diversity	Boehringer Ingelheim	None identified	Comments noted. No action required.
	Janssen	No equality issues have been identified.	Comments noted. No action required.
	AstraZeneca	No comment	No action required.
	Merck Sharp and Dohme	No comment	No action required.
Innovation	Janssen	Janssen consider an insulin-independent mechanism of action such as that of canagliflozin innovative as unlike some other therapeutic options, its clinical utility remains even as pancreatic function declines over the course of the disease. The urinary glucose excretion resulting from SGLT2 inhibition not only lowers plasma glucose, but also results in: 1) an osmotic diuresis leading to a reduction in systolic blood pressure and 2) a loss of calories and therefore a reduction in body weight. SGLT-2 inhibition offers several advantages. Acting independently of insulin, these agents should not confer a risk of hypoglycaemia and could be employed as monotherapy or in combination with other agents. Given their mechanism of action, these agents should be effective in patients with any degree of insulin resistance or impaired β-cell function. [reference: http://clinical.diabetesjournals.org/content/32/1/4.full]	Comments noted. The innovative nature of the interventions will be considered as part of the full appraisal.
	AstraZeneca	No comment.	No action required.

Section	Consultees	Comments	Action
Other considerations	Janssen	No comment.	No action required.
	AstraZeneca	None	Comments noted. No action required.
	Merck Sharp and Dohme	No comment	No action required.
Questions for consultation	Boehringer Ingelheim	*Which treatments are considered to be established clinical practice in the NHS for use as monotherapy in type 2 diabetes?* Metformin, insulin, Sulphonylureas, DPP4i, TZDs (low) and rapid acting secretagogues/acarbose (very low) *Should rapid acting insulin secretagogues, acarbose or DPP-4 inhibitors be included as comparators?* Of these just DPP4 inhibitors should be considered, use of acarbose is very low and rapid acting secretagogues are recommended in a different clinical setting to SGLT2i in CG 87 *Are there any subgroups of people in whom canagliflozin, dapagliflozin and empagliflozin are expected to be more clinically effective and cost effective or other groups that should be examined separately?* Subgroup analysis did not identify treatment effect by subgroups, therefore empagliflozin and presumably the other SGLT2i are not anticipated to be of differing efficacy across subgroups *Where do you consider canagliflozin, dapagliflozin and empagliflozin will fit into the existing NICE pathway, diabetes?* It should fit with other oral treatments as alternatives to metformin intolerance or lack of response.	Comments noted. The comparators section has been updated to include DPP-4 inhibitors, pioglitazone and repaglinide.

Section	Consultees	Comments	Action
	Janssen	Janssen does not believe that there is any clinical need to review separate patient groups within the suggested population, in the scope. For example post-hoc subgroup analyses for BMI showed that the efficacy of canagliflozin in terms of change in HbA1c was not impacted by baseline BMI levels. It is proposed that canagliflozin will fit into the NICE pathway for treatment of T2DM in line with its marketing authorisation, specifically: Invokana is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as: <u>Monotherapy</u> When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. Data for monotherapy use of canagliflozin to treat adults with T2DM is available in published peer review journals and posters at international congresses.	Comments noted. No action required.
Additional comments on the draft scope.	Boehringer Ingelheim	None	Comments noted. No action required.
	Janssen	No additional comments to the above.	Comments noted. No action required.

Section	Consultees	Comments	Action
	AstraZeneca	While AstraZeneca welcomes the appraisal of medicines via the technology appraisals programme, on this occasion since monotherapy is not the key clinical treatment area for SGLTs, we feel that assessment of this class of oral anti-diabetic agents as monotherapy for the treatment of type 2 diabetes would be best managed within the current review of the NICE Type 2 diabetes guideline (CG 87) rather than the MTA process. This will ensure that guidance is issued to the NHS in a timely manner whilst also making best use of NICE resources.	Comments noted. Scoping workshop attendees noted that following referral, the interventions had only been partially appraised (as combination therapy). Therefore the monotherapy part of the referral still required appraisal. Scoping workshop attendees agreed that the proportion of the type 2 diabetes population that would be affected by this appraisal was small. However, given this is a small proportion of a large population this would be an important appraisal for a significant amount of people. NICE delayed the appraisal so the scope could take into account any updated draft recommendations from the review of the diabetes clinical guideline.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

Canagliflozin, dapagliflozin and empagliflozin for the monotherapy treatment of type 2 diabetes [ID756]

Response to consultee and commentator comments on the provisional matrix of consultees and commentators

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Suggestion to add British Renal Society	Janssen		Not included	This organisation's interests are not directly related to the appraisal topic. The British Renal Society has not been included in the matrix of consultees and commentators.

2.	Add Aspire Pharma	NICE secretariat		Added	This organisation's interests are directly related to the appraisal topic. Aspire Pharma has been included in the matrix of consultees and commentators as a comparator company.
3.	Add Novo Nordisk	NICE secretariat		Added	This organisation's interests are directly related to the appraisal topic. Novo Nordisk has been included in the matrix of consultees and commentators as a comparator company.
4.	Add Waymade Healthcare	NICE secretariat		Added	This organisation's interests are directly related to the appraisal topic. Waymade Healthcare has been included in the matrix of consultees and commentators as a comparator company.

5.	Remove Bayer	NICE secretariat		Removed	This organisation's interests are not directly related to the appraisal topic. Bayer has been removed from the matrix of consultees and commentators as a comparator company.
6.	Remove Health Research Authority	Health Research Authority.		Removed	This organisation no longer wishes to be included in TA appraisals. Health Research Authority has been remove from the matrix of consultees and commentators under relevant research group.