National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Empagliflozin combination therapy for treating type 2 diabetes

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Boehringer Ingelheim Ltd/ Eli Lilly	Empagliflozin is an appropriate topic for NICE to appraise. Diabetes is a key issue for the NHS. It is estimated there will be almost 5 million people with type 2 diabetes by 2025. In addition, people are being diagnosed with diabetes at a younger age and are living longer with the condition. SGLT-2s offer an innovative treatment that acts on the re-absorption of glucose through the kidneys which differs from other existing anti-diabetic treatments. SGLT-2s offer HbA1c control, with additional benefits on weight reduction, low risk of hypoglycaemia and reduced systolic blood pressure. Given the growing complexity of diabetes SGLT-2s offer a significant benefit to people with diabetes.	Comment noted. No changes to the scope required.
	Merck Sharp & Dohme	No comments	Response noted. No changes to the scope required.
	Royal College of Pathologists	Yes	Comment noted. No changes to the scope required.
Wording	Boehringer Ingelheim Ltd/ Eli Lilly	This is appropriate.	Comment noted. No changes to the scope required.
	Merck Sharp & Dohme	No comments	Response noted. No changes to the scope required.

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	Royal College of Pathologists	Yes	Comment noted. No changes to the scope required.
Timing Issues	Boehringer Ingelheim Ltd/ Eli Lilly	It is essential that timely guidance is issued to the NHS on empagliflozin as it is due to be licensed [redacted] and there will be multiple SGLT-2s available	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Merck Sharp & Dohme	No comments	Response noted. No changes to the scope required.
Additional comments on the draft remit		No response received	

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Boehringer Ingelheim Ltd/ Eli Lilly	No comments	Response noted. No changes to the scope required.
	Merck Sharp & Dohme	No comments	Response noted. No changes to the scope required.
	Royal College of Pathologists	Background provides a good summary of existing therapies as recommended by NICE. It should also refer to the other SGLT-2 drugs	Comment noted. The background section of the scope has been updated to include NICE guidance on dapagliflozin.
The technology/ intervention	Boehringer Ingelheim Ltd/ Eli Lilly	This is appropriate; evidence presented will depend on final licensed indications.	Comment noted. No changes to the scope required.
	Merck Sharp & Dohme	No comments	Response noted. No changes to the scope required.
	Bristol-Myers Squibb / AstraZeneca	The description of the empagliflozin add-on to insulin trial is incorrect. The only type of insulin used was basal insulin, and there is no data for use in combination with other insulin types. We suggest revised to "Empagliflozin alone or in combination with oral anti-diabetic agents and/or insulin" as monotherapy is not a patient group of interest to the NHS for the SGLT-2 inhibitors	Comment noted. At scoping workshop the manufacturer confirmed that in the clinical trials patients on any type of insulin were included and clinical specialists confirmed that it was not necessary to specify the type of insulin in the scope. It was also agreed that use in monotherapy would not be considered in this appraisal. The scope has been updated.
	Royal College of Pathologists	Yes	Comment noted. No changes to the scope required.

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Population	Boehringer Ingelheim Ltd/ Eli Lilly	We consider that monotherapy should remain as part of the scope. There will be sufficient data to support an appraisal in this indication. In addition, there is a clinical need for people unable to take metformin and where there is a concern over the hypoglycaemia risk and weight gain associated with SUs and the weight reduction could benefit them.	Comment noted. At the scoping workshop it was agreed that use in monotherapy would not be considered in this appraisal. The scope has been updated.
	Merck Sharp & Dohme	We do not believe that the scope should include monotherapy (see our response to the consultation question "Is it apppropriate to include in the scope the use of empagliflozin as monotherapy?")	Comment noted. At the scoping workshop it was agreed that use in monotherapy would not be considered in this appraisal. The scope has been updated.
	Bristol-Myers Squibb / AstraZeneca	1. We suggest removing monotherapy from the population as this is not a patient group of interest to the NHS for the SGLT-2 inhibitors 2. Under 'Dual therapy', we note that most guidelines in the world (NICE/SMC/EASD/ADA) only recommend a sulphonylurea as first line for a limited period (namely to control osmotic symptoms) and then metformin is preferred. Alternatively, SU monotherapy is reserved for the small group of metformin-intolerant patients. As a consequence, this indication (add-on to sulphonylurea) has limited benefit to the NHS and we suggest is removed from the scope. 3. Under 'Triple therapy', the triple combinations with sulphonylurea excluding metformin have not been studied and should not be in scope. 4. Under 'Triple therapy', please include SGLT-2 inhibitors in the list of comparators ("metformin or a sulfonylurea in combination with a thiazolidinedione, a DPP-4 inhibitor, a GLP-1 analogue, or a SGLT-2 inhibitor"). 5. Under 'Triple therapy', the combination of empagliflozin and GLP-1 analogue has not been studied clinically and so this should not be in the scope. 6. Under 'add-on therapy to insulin', the scope should be limited to 'add-on to basal insulin only' as there are no data for empagliflozin	Comments noted. 1. At the scoping workshop it was agreed that use in monotherapy would not be considered in this appraisal. The scope has been updated. 2. NICE clinical guideline 87 recommends dual therapy with metformin and sulphonylureas when blood glucose control remains or becomes inadequate with metformin. In the context of dual therapy it does not specify treatment for a limited period or for osmotic control only. Clinical specialists at the scoping workshop agreed that metformin and sulphonylureas was the most commonly used combination for dual therapy in clinical practice. 3. The draft scope outlines the population likely to be considered

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		with other insulin types.	for the new technology in the context of established clinical practice and should not necessarily be the trial population. 4. SGLT-2 inhibitors are not included under the 'triple therapy' population because dapagliflozin is not recommended in a triple therapy regimen in combination with metformin and a sulphonylurea in NICE TA288 and canagliflozin is subject to on-going NICE appraisal. 5. The population in the scope refers to the established treatments that are licensed or approved for use at each stage of the clinical pathway for type 2 diabetes and do not necessarily reflect the treatment received by the patients in the comparator arm in the relevant empagliflozin trials. 6. At the scoping workshop the manufacturer confirmed that in the clinical trials patients on any type of insulin were included and clinical specialists did not think it was necessary to specify the type of insulin.
	Royal College of Pathologists	Yes	Comment noted. No changes to the scope required.
Comparators	Boehringer Ingelheim Ltd/	Monotherapy should remain within the scope to allow empagliflozin to be appraised within its full marketing authorisation and potentially offer	Comment noted. At the scoping workshop clinical specialists did not

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	Eli Lilly	an alternative to people who are not appropriate or unwilling to take an SU. The options for dual and triple and insulin combination therapy are appropriate.	consider that empagliflozin would be used as a monotherapy given the currently available treatment options for this population. It was also noted that the monotherapy population was not included in the appraisals of dapagliflozin or canagliflozin for type 2 diabetes. The intervention, population and comparators in the scope have been amended to reflect this.
	Merck Sharp & Dohme	We do not believe that the scope should include monotherapy (see our response to the consultation question "Is it appropriate to include in the scope the use of empagliflozin as monotherapy?"). However if it is decided that the use of empagliflozin as monotherapy should remain in the scope, DPP-4 inhibitors and thiazolidinediones should be included as monotherapy comparators.	Comment noted. At the scoping workshop it was agreed that use in monotherapy would not be considered in this appraisal. The scope has been updated.
	Bristol-Myers Squibb / AstraZeneca	1. Under 'Monotherapy', we suggest removing the sulphonylurea monotherapy comparator as this is not a patient group of interest to the NHS for the SGLT-2 inhibitors (see under 'Population' above). If monotherapy remains in the scope, other medicines licensed for monotherapy use (e.g., DPP4s, dapagliflozin) should be included as comparators. 2. Under 'Triple therapy', sulphonylurea should also be a comparator for the EMP/MET/PIO combination, as MET/PIO/SU is the most common triple therapy combination in the UK, as recommended by NICE Clinical Guideline CG87 3. Under 'add-on therapy to insulin', this should be changed to 'add-on therapy to basal insulin' as empagliflozis has not been studied in combination with other insulin types. 4. Under 'add-on therapy to insulin', the comparators should be expanded to include injectable GLP-1. Exenatide (Byetta) is licensed	Comments noted. 1. At the scoping workshop it was agreed that use in monotherapy would not be considered in this appraisal. The scope has been updated. 2. At the scoping workshop, it was agreed that in clinical practice, triple therapy with empagliflozin, metformin and pioglitazone will be reserved for those patients who are unable to take sulphonylurea. No action required. 3. At the scoping workshop the manufacturer confirmed that in the

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		for this indication. Prandial insulin should also be a comparator. 5. NICE guidance on dapagliflozin has now been published (TA288, June 2013)	clinical trials patients on any type of insulin were included and clinical specialists did not consider that it was necessary to specify the type of insulin. Workshop attendees agreed that no changes to the scope were required. 4. At the scoping workshop the clinical specialists did not consider that it was necessary to specify the type of insulin in the scope. NICE clinical guideline 87 recommends exenatide (twice-daily) only as a triple therapy in combination with metformin and sulfonylurea when control of blood glucose remains or becomes inadequate. At the scoping workshop it was noted that exenatide (twice-daily) was not licensed for use with insulin at the time of guideline development and is indicated as adjunctive therapy to basal insulin only. For consistency with previous scopes on SGLT-2 inhibitors, it was agreed that comparator for add-on therapy to insulin should remain unchanged. No changes to the scope were required. 5. The scope has been updated to include guidance in TA 288.
	Janssen-Cilag	For the Triple therapy, dapagliflozin should be removed as a comparator to empagliflozin, metformin and pioglitazone as	Comment noted. The scope has been updated to reflect recommendations for

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	Ltd.	dapagliflozin is contraindicated from combination with pioglitazone.	dapagliflozin in TA 288.
	Royal College of Pathologists	Yes, although also compare with acarbose, both because this also still appears in the NICE pathway and is also a regulator of postprandial hyperglycaemia	Comment noted. At the scoping workshop it was agreed that use in monotherapy would not be considered in this appraisal. The intervention, population and comparators of the scope have been updated to reflect this.
Outcomes	Boehringer Ingelheim Ltd/ Eli Lilly	These are appropriate	Comment noted. No changes to the scope required.
	Merck Sharp & Dohme	We suggest that the following should be included as additional outcomes: Cancer Decline in eGFR	Comment noted. Attendees at the scoping workshop did not consider it appropriate to include either 'cancer' or 'decline in eGFR' as outcomes since if these are related outcomes they would be considered under safety. Data for these outcomes may be included in submissions to NICE as part of the adverse effects of treatment outcome. No changes to the scope required.
	Royal College of Pathologists	Yes	Comment noted. No changes to the scope required.
Economic analysis	Boehringer Ingelheim Ltd/ Eli Lilly	No comment	Response noted. No changes to the scope required.
	Merck Sharp & Dohme	No comments	Response noted. No changes to the scope required.

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Equality and Diversity	Boehringer Ingelheim Ltd/ Eli Lilly	No comment	Response noted. No changes to the scope required.
	Merck Sharp & Dohme	No comments	Response noted. No changes to the scope required.
Innovation	Boehringer Ingelheim Ltd/ Eli Lilly	Empagliflozin is likely to be licensed as a single dose in contrast to dapagliflozin and canagliflozin which have multiple doses. Hence, it does not require any dose adjustment due to co-morbidities, such as renal impairment. Therefore, there may be process of care benefits from reduced monitoring or consultations in comparison to other SGLT-2s.	Comment noted. The Committee will consider the innovative aspect of empagliflozin during the course of the appraisal. No changes to the scope required.
	Bristol-Myers Squibb / AstraZeneca	Difficult to support innovation when it is the third molecule in this class to market.	Comment noted. The Committee will consider the innovative aspect of empagliflozin during the course of the appraisal. No changes to the scope required.
Other considerations	Boehringer Ingelheim Ltd/ Eli Lilly	No comments	Response noted. No changes to the scope required.
	Merck Sharp & Dohme	We suggest that a subgroup based on renal function should also be considered (for example, it will be important to consider patients with eGFR <30).	Comment noted. At the scoping workshop the manufacturer confirmed that empagliflozin is not likely to be licensed for use in people who have severe renal impairment. Attendees did not consider this an appropriate subgroup. No changes to the scope required.
	Janssen-Cilag Ltd.	The subgroup analysis by patients with renal impairment is suggested.	Comment noted. At the scoping workshop the manufacturer confirmed that empagliflozin is not likely to be

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			licensed for use in people who have severe renal impairment. Attendees did not consider this an appropriate subgroup. No changes to the scope required.
	Royal College of Pathologists	consider use in patients with chronic kidney disease	Comment noted. At the scoping workshop the manufacturer confirmed that empagliflozin is not likely to be licensed for use in people who have severe renal impairment. Attendees therefore did not consider this an appropriate subgroup. No changes to the scope required.
NICE Pathways	Boehringer Ingelheim Ltd/ Eli Lilly	Empagliflozin fits under several sub headings within managing type 2 diabetes, and blood glucose lowering therapy for type 2 diabetes. For mono therapy it is an alternative to metformin along with SUs. Empagliflozin could also be included within : 'Considering dual therapy', 'Considering triple therapy' and 'Intensifying insulin regimen or considering adding other drugs'	Comment noted. No changes to the scope required.
	Bristol-Myers Squibb / AstraZeneca	Current positioning of DPP4 inhibitors and dapagliflozin as add-on metformin and add-on insulin. Current positioning of pioglitazone, GLP-1s and DPP4-inhibitors for triple therapy	Comment noted. No changes to the scope required.
Questions for consultation	Boehringer Ingelheim Ltd/ Eli Lilly	*NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.* It is appropriate for empagliflozin to be assessed through the STA process. Firstly it allows for guidance to be issued within six months of	Comment noted. The scoping workshop attendees agreed that the STA process was appropriate.

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		marketing authorisation. Secondly, there is an opportunity for empagliflozin to be considered for inclusion in the update to the type 2 diabetes in adults' clinical guideline before it goes out for consultation. This would enable empagliflozin to be included along with canagliflozin and dapagliflozin within the treatment pathway.	
	Merck Sharp & Dohme	In response to the consultation question "Is it appropriate to include in the scope the use of empagliflozin as monotherapy?" To ensure consistency with the recently published single technology appraisal for dapagliflozin (TA288), we do not believe that the use of empagliflozin for monotherapy should be included in the scope for the proposed technology appraisal. Dapagliflozin, like empagliflozin, has been studied in clinical trials as monotherapy. Despite this the STA for dapagliflozin did not consider its use as monotherapy. Consequently we suggest the same population restrictions should apply to empagliflozin. In response to the consultation question "Have the most appropriate comparators for empagliflozin for the treatment of type 2 diabetes been included in the scope? Are the comparators listed routinely used in clinical practice?" We agree that all comparators listed are appropriate, providing their usage is in line with the recommendations as stated in the prevailing NICE guidance documents, as listed below: CG66/87:Type 2 diabetes - the management of type 2 diabetes TA203:Liraglutide for the treatment of type 2 diabetes mellitus TA 248: Exanatide prolonged release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes TA288 Dapagliflozin in combination therapy for treating type 2	Comment noted. At the scoping workshop it was agreed that use in monotherapy would not be considered in this appraisal. The scope has been updated. Comment noted. No changes to the scope required.

Section	Consultees	Comments	Action
		diabetes	
	Bristol-Myers Squibb / AstraZeneca	Q1. Is it appropriate to include the use of empagliflozin as monotherapy in the scope? We do not believe it is the best use of limited NHS resources to appraise empagliflozin as monotherapy, as it will be unrealistic to displace metformin. This is consistent with previous decisions made at NICE scoping workshops for dapagliflozin and canagliflozin appraisals Q2. The comparators in the scope include combinations that are reflected in NICE guidance or NICE clinical guidelines. Have the most appropriate comparators for empagliflozin for the treatment of type 2 diabetes been included in the scope? Are the comparators listed routinely used in clinical practice? All the comparators are consistent with NICE guideline CG87. We note that an update to the T2DM guidelines is due to be published in August 2014 and would recommend these comparators be revisited alongside the updated guidelines at the decision problem meeting, and the Appraisal Committee meeting, in line with the updated Methods Guide. Q3. Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? We believe the evaluation of empagliflozin should stratify patients by mild, moderate and severe renal impairment. A subgroup of elderly patients should also be considered.	1. Comment noted. At the scoping workshop it was agreed that use in monotherapy would not be considered in this appraisal. The scope has been updated. 2. The scope identifies all potentially relevant comparators, taking into account issues likely to be considered by the Appraisal Committee when selecting the most appropriate comparator. The Appraisal Committee will make judgements on the appropriateness and relevance of comparator technologies in accordance with updated Methods Guide. 3. The scoping workshop attendees agreed that it would not be appropriate to consider subgroups based on age. Attendees also heard from the manufacturer that they did not expect empagliflozin to be used in patients with severe renal impairment.
Additional comments on the draft scope.	Boehringer Ingelheim Ltd/ Eli Lilly	We would strongly suggest that empagliflozin be scheduled into NICEs work program as soon as possible since not only would it allow timely guidance for the NHS, but also to allow empagliflozin to be included in the updated type 2 diabetes in adults clinical guideline	Comment noted. No changes to the scope required.

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

Royal College of Nursing
Servier Laboratories Ltd
Society for Endocrinology

NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE

Single Technology Appraisal (STA)

Empagliflozin combination therapy for treating type 2 diabetes [ID641]

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

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.	Add British Renal Association	Janssen-Cilag		Not added	This organisation's interests are not closely related to the appraisal topic. Empagliflozin is not used during kidney failure
2.	Add Kidney Association	Janssen-Cilag		Not added	This organisation's interests are not closely related to the appraisal topic. Empagliflozin is not used during kidney failure