National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Dapagliflozin for treating chronic kidney disease ID3866

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	AstraZeneca	Yes, this topic is appropriate for NICE appraisal.	Comment noted. No action required.
	Primary Care Diabetes Society	Yes. Despite maximal tolerated RAAS usage, there is still residual burden of CKD over the past 2 decades.	Comment noted. No action required
	The Renal Association (endorsed by Royal College of Physicians)	It is our view that the evidence that has emerged over the last five years indicates that the SGLT2I class has a significant cardiorenal protective effect that is quite separate from the glycaemic effectiveness of these drugs. It is therefore very appropriate and indeed important that this appraisal is undertaken in order to ensure that patients who could benefit are given access to appropriate treatment.	Comment noted. No action required
	Novartis Pharmaceuticals UK Limited	Novartis considers it appropriate to refer this topic to NICE for appraisal	Comment noted. No action required
Wording	AstraZeneca	No changes are required to the wording of the remit. [redacted]	Comment noted. No action required
	Primary Care Diabetes Society	Yes	Comment noted. No action required

Section	Consultee/ Commentator	Comments	Action
	The Renal Association (endorsed by Royal College of Physicians)	Wording and remit are appropriate	Comment noted. No action required
	Novartis Pharmaceuticals UK Limited	No comments.	Comment noted. No action required
Timing Issues	AstraZeneca	The lack of new treatments for CKD over the last few decades has highlighted the substantial unmet need for new options to slow the progression of CKD, prevent progression to end-stage kidney disease (ESKD) and prevent premature mortality in patients with CKD.[1] The DAPA-CKD trial was stopped early due to overwhelming efficacy. The trial demonstrated that dapagliflozin, as add-on therapy to standard care, offers significant reductions in the primary composite outcome of sustained decline in estimated glomerular filtration rate (eGFR) ≥50%, ESKD or death from renal or cardiovascular (CV) causes and all-cause mortality in patients with CKD with and without type 2 diabetes mellitus (T2DM) compared with current standard care alone.[2] The trial also demonstrated that treatment with dapagliflozin, as add-on therapy to standard care, led to significant reductions in the secondary composite endpoint of CV death or hospitalisation due to heart failure (HF); the secondary composite renal endpoint of a sustained decline in eGFR ≥50%, reaching ESKD (including the need for chronic dialysis or kidney transplant) or death from renal causes; and the secondary endpoint of all-cause mortality, compared to standard care. Reducing the risk of these events will improve outcomes for patients with CKD and reduce the burden of CKD on the National Health Service (NHS). Therefore, AstraZeneca requests the appraisal to be scheduled as soon as possible and in line with NICE's principle of appraisal timelines based on Section 3.[18] of the Voluntary Scheme for Branded Medicines Pricing and Access agreement.[3] Timely assessment and approval of dapagliflozin will result in meaningful benefits to patients with CKD as soon as possible	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.

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		following marketing authorisation which is anticipated from the Medicines and Healthcare products Regulatory Agency (MHRA) on [redacted] *References provided but not included here.*	
	Primary Care Diabetes Society	There is no need to delay this, as the drug is already approved for use in diabetes	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	The Renal Association (endorsed by Royal College of Physicians)	As stated there is a significant body of evidence that demonstrates the beneficial effects that the SGLT2i class and dapagliflozin in particular have in slowing down or preventing cardio renal complications when used in addition to standard the care. It is important that there is a rapid definition of the groups of patients who are most likely to benefit from this intervention and that they are given access to this treatment.	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	Novartis Pharmaceuticals UK Limited	An update of the NICE guideline 'Chronic kidney disease: assessment and management' is currently ongoing. It may be advisable to take the timelines of the guideline update into account for the timing of this technology appraisal, to allow the most recent consensus on CKD management to be taken into consideration.	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the

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			marketing authorisation for a technology is granted. The committee will consider all available information at the time of the committee meeting. Please see Section 3.1 of NICE Guide to the processes of technology appraisal for further information on appraisal timelines. No action required.
Additional comments on the draft remit	AstraZeneca	None	Comment noted. No action required
	Primary Care Diabetes Society	No comments	Comment noted. No action required
	The Renal Association (endorsed by Royal College of Physicians)	No comments	Comment noted. No action required
	Novartis Pharmaceuticals UK Limited	No comments	Comment noted. No action required

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	AstraZeneca suggests the following additions/amendments to the background information presented within the draft scope: • The scope states “Prevalence also increases with age, and around 30% of people aged 75 and over will have stage 3-5 CKD”. AstraZeneca requests that the scope highlights that CKD also impacts patients under the age of 75 years old: the UK Renal Registry report states the median age of patients undergoing renal replacement therapy (RRT) is 59.5 years old.[4] • The statement that “diabetes is associated with around 40% of cases of CKD” has been misquoted from the original source. The source reports “diabetes has been established as the cause of around a quarter of all CKD cases”.5 It is estimated that 34% of people with CKD also have comorbid type 2 diabetes (T2DM).[6] • In addition to CV disease, it important to note that CKD is also associated with a greater risk of premature mortality compared to the general population. In England, there are estimated to be 40,000 to 45,000 premature deaths each year in people with CKD.[1] • It is also important to note that the prevalence of CKD and RRT is increasing, and the burden associated with CKD is therefore predicted to increase in the future: there was a 2.8% increase in the number of patients receiving RRT between 2017-2018 and the annual healthcare costs associated with CKD in the UK are projected to increase from £12.7 billion in 2020 to £16.7 billion in 2025.[4, 7] • The NICE Clinical Guideline for CKD in adults (CG182) does not specifically refer to atorvastatin. Instead, statins are referred to as a class of pharmacotherapy that may be prescribed in patients with CKD – the statement about the	Comments noted. The background section of the draft scope is intended to give a broad introduction to the condition and is therefore not exhaustive. However, the following updates have been made to the scope: - Clarified that diabetes causes around a quarter of all CKD cases. - Included premature mortality rates for CKD. - Removed atorvastatin and clarified that statins, not steroids, are a treatment option. - Clarified that apixaban is an anticoagulant.

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		recommendation for statin use should therefore be amended. Furthermore, atorvastatin is a statin, not a steroid as described in the draft scope. • Finally, the NICE Clinical Guideline for CKD in adults (CG182) also refers to both antiplatelet drugs and anticoagulants; apixaban should be referred to as an anticoagulant instead of an antiplatelet in the scope. *References provided but not included here.*	
	Primary Care Diabetes Society	The background is mostly accurate but Atorvastatin is not a steroid, it is a statin, and apibaxan is an anticoagulant, not antiplatelet	Comment noted. The scope has been updated to replace steroids with statins and clarify that apixaban is an anticoagulant.
	The Renal Association (endorsed by Royal College of Physicians)	Whilst the background is essentially accurate it does not clearly highlight the problem which is that that there is a need to reduce cardio renal complications in this group of patients who have already identified themselves as having underlying kidney disease.	Comment noted. The scope has been updated to include the following wording based on NICE Clinical Guideline 182: *"Treatment aims to prevent or delay progression of CKD, reduce or prevent complications, and reduce the risk of cardiovascular disease"*.
	Novartis Pharmaceuticals UK Limited	We propose to replace "end-stage kidney disease (ESKD)" with "kidney failure", as the latest preferred term.	Comment noted. The wording of the scope has been updated as suggested.

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		The summary of recommendations of the NICE CKD clinical guideline in the background section reflects contents of the current guideline version, some of which are expected to change in the updated guideline. For instance, the draft recommendation for management of hypertension in people with CKD and an ACR >30 mg/mmol does not mention direct renin inhibitors (section 1.6.5 of the draft guideline). In the summary of guideline recommendations, atorvastatin is incorrectly referred to as a steroid. This has to be corrected to 'statin'. *References provided but not included here.*	
The technology/ intervention	AstraZeneca	Whilst the mechanism of action of dapagliflozin in CKD is not yet fully understood, a putative mechanism has been hypothesised whereby sodium glucose transport protein 2 (SGLT2) inhibition by dapagliflozin reduces the reabsorption of sodium and glucose in the proximal tubule of the kidney, leading to restoration of tubuloglomerular feedback, vasoconstriction of the afferent arteriole and reduction in blood flow through the glomerulus, causing a reduction in intraglomerular pressure and glomerular hyperfiltration which provides renal protection.[8] AstraZeneca requests that the description of the technology is amended to include this assumed mechanism of action. The <u>description of the technology</u> is largely accurate but AstraZeneca requests that the phrase "who are stable on optimised standard care" is changed to "who are receiving individually optimised standard care" to avoid misinterpretation and to make clear that the term	Comments noted. The mechanism of action for dapagliflozin in CKD is not confirmed therefore no changes have been made to the scope. The description of the technology has been updated with the suggested wording.

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		stable refers to the dose of standard care rather than the disease itself. CKD is a progressive disease and even patients receiving optimised standard care have a residual risk of progression and adverse outcomes.[9] AstraZeneca further requests that the description of the intervention is updated to "Dapagliflozin 10mg per day in combination with optimised standard care (which may include treatment with an angiotensin converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB])." The anticipated licensed dose for dapagliflozin in this indication is 10 mg per day, and standard care for patients with CKD comprises individually optimised therapy which may include a variety of treatment strategies. These include CV risk management using statins and antiplatelets, management of underlying T2DM and/or hypertension, and ACE inhibitors or ARBs for the management of disease progression.[10] Although the majority of patients with CKD receive ACE inhibitor or ARB therapy in clinical practice, these medications are only recommended for the following subgroups of patients with CKD: • Patients with comorbid diabetes and a urine albumin to creatinine ratio (uACR) of 3 mg/mmol or more • Patients with hypertension and a uACR of 30 mg/mmol or more • Patients with a uACR of 70 mg/mmol or more (irrespective of hypertension or CV disease)	The dose of dapagliflozin appraised by NICE will be in line with its expected marketing authorisation and is not specified in the description of the intervention. The description of the intervention has been left broad to allow for variation in individually optimised standard care. No changes have been made to the scope.

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		Furthermore, some patients may not be able to tolerate ACE inhibitors or ARBs due to the associated risk of hyperkalaemia and hypotension.[11] Therefore, a proportion of patients with CKD in clinical practice do not receive ACE inhibitor or ARB therapy, but would still benefit from the cardiorenal protective effects of dapagliflozin, a viewpoint supported by UK clinical experts.[12] AstraZeneca therefore requests that the description of the technology is amended to reflect this, as above. *References provided but not included here.*	
	Primary Care Diabetes Society	Yes, this is accurate	Comment noted. No action required
	The Renal Association (endorsed by Royal College of Physicians)	This is accurate	Comment noted. No action required
	Novartis Pharmaceuticals UK Limited	Dapagliflozin is being studied in the DAPA-CKD trial as an addition to standard of care. Patients enrolled in the trial were required to be on a stable, maximum tolerated daily dose of an ACE inhibitor or ARB, if not medically contraindicated. However, the published trial protocol does not make reference to "individually optimised standard care" and it is unclear whether patients were taking treatments other than	Comment noted. In line with consultation comments from the company, the technology section has been updated to confirm that patients included in the trial were taking '*individually optimised standard care'.*

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		ACE inhibitors or ARBs, such as statins or diuretic medication, at an individually optimised dose. The draft scope describes the trial population as patients "who are stable on optimised standard care", suggesting that these patients' kidney disease was stable at time of study enrolment. According to the study inclusion criteria, patients had to be on a stable dose of an ACE inhibitor or ARB for at least 4 weeks before study visit 1, but did not necessarily have stable kidney disease prior to randomisation. For inclusion in the study, patients were required to have evidence of increased albuminuria for at least 3 months. We therefore propose to modify the sentence in the section "The technology" as follows: *"It* [dapagliflozin] *is being studied in combination with ~~individually optimised~~ standard care in a randomised controlled trial compared with placebo with ~~individually optimised~~ standard care, in adults with an eGFR between 25 and 75 mL/min/1.73m^2 and increased albuminuria for 3 months or more who are on a stable ~~on optimised standard care with the~~ maximum tolerated dose of an ACE inhibitor or ARB~~s~~."* In the Intervention section, we propose to modify the sentence as follows: *"Dapagliflozin in combination with ~~optimised~~ standard care (including treatment with an ACE inhibitor or ARB at a stable, maximally tolerated dose)."* It could be added to the description of the trial that patients with a history of organ transplantation were excluded. *References provided but not included here.*	

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Population	AstraZeneca	The patient population is listed as “Adults with chronic kidney disease who are stable on individually optimised standard care”. As above, AstraZeneca requests that this is rephrased to “adults with chronic kidney disease who are receiving individually optimised standard care”, with “stable” removed. CKD is a progressive disease and even patients receiving optimised standard care have a residual risk of progression, morbidity and mortality.[9] These patients would benefit from additional treatment options to address this residual risk. *References provided but not included here.*	Comment noted. The scope has been updated with the suggested wording.
	Primary Care Diabetes Society	The population indicated is too broad. Their study did not include Autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis and these are all causes of CKD Type 1 diabetes mellitus	Comment noted. The committee will appraise the treatment within its marketing authorisation. The population has been left broad to accommodate potential changes of wording of the marketing authorisation. No changes have been made to the scope.
	The Renal Association (endorsed by Royal College of Physicians)	The wording of the technology section implies that dapagliflozin is being assessed only in people who are stable on standard care whereas it is being studied and indeed may be most useful in those individuals who are demonstrating evidence of deterioration despite standard of care.	Comment noted. The wording of the scope has been updated to clarify that the population of interest is “*Adults with chronic kidney disease who are receiving individually optimised standard care”*

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	Novartis Pharmaceuticals UK Limited	As highlighted above, the trial population included adults with chronic kidney disease who were on a stable dose of an ACE inhibitor or ARB, while the draft scope wording suggests that patients' kidney disease was stable. We therefore propose to modify the population in the scope to: "*Adults with chronic kidney disease who are ~~stable~~ on ~~individually optimised~~ standard care (including a stable, maximally tolerated dose of an ACE inhibitor or ARB)*". *References provided but not included here.*	Comment noted. The wording of the scope has been updated to clarify that the population of interest is "*Adults with chronic kidney disease who are receiving individually optimised standard care"*
Comparators	AstraZeneca	The comparator is listed as established clinical management without dapagliflozin. AstraZeneca agrees that this comparator is appropriate.	Comment noted. No action required.
	Primary Care Diabetes Society	YES	Comment noted. No action required.
	The Renal Association (endorsed by Royal College of Physicians)	The standard of care is defined according to the NICE CKD guidelines and is generally implemented in people with CKD however there are issues in relation to the maximal dose of inhibitors of the renin angiotensin aldosterone system that some individuals can tolerate.	Comment noted. No action required.
	Novartis Pharmaceuticals UK Limited	No comments.	Comment noted. No action required.

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Outcomes	AstraZeneca	Yes, the outcomes listed are appropriate and represent those most clinically relevant to CKD. However, AstraZeneca requests that “serum creatinine” is replaced with “estimated glomerular filtration rate (eGFR)” as eGFR is a more complete measure of kidney function that incorporates serum creatinine as well as other relevant factors.[13] A sustained decline in eGFR of ≥50% was also a component of the primary endpoint in the DAPA-CKD trial.2 *References provided but not included here.*	Comment noted. The scope has been updated with the suggested wording.
	Primary Care Diabetes Society	YES	Comment noted. No action required.
	The Renal Association (endorsed by Royal College of Physicians)	For the outcome measures it is important to distinguish between sustained changes in kidney function (creatinine or eGFR change) and acute changes that may have no clinical relevance. There also needs to be a clear understanding as to what is meant by adverse outcomes and more clearly how these would be monitored.	Comment noted. Sustained changes in kidney function would be captured by the existing outcome ‘markers of disease progression’. The outcomes listed in the scope are not exhaustive, companies are encouraged to provide all relevant data that will be informative for the appraisal.

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	Novartis Pharmaceuticals UK Limited	We propose to change “renal replacement” to “kidney replacement therapy” and “ESKD” to “kidney failure”, in order to use the latest preferred terminology. *References provided but not included here.*	Comment noted. The scope has been updated with the suggested wording.
Economic analysis	AstraZeneca	AstraZeneca has no comments relating to the economic analysis for this appraisal. An economic model is being constructed in Microsoft Excel to estimate the cost-effectiveness of dapagliflozin vs standard care from a UK NHS and personal social services perspective. The cost-effectiveness of treatments will be expressed in terms of cost per quality adjusted life year (QALY) and a lifetime time horizon will be adopted in order to capture all relevant differences in costs and outcomes between the technologies being compared.	Comment noted. No changes to scope necessary.
	Primary Care Diabetes Society	The economic analysis will be needed to demonstrate the cost impact.	Comment noted. No action required.
	The Renal Association (endorsed by Royal College of Physicians)	We are in agreement that the time horizon needs to be sufficient to measure the medium term benefits of reduction in cardiovascular and end-stage renal failure outcomes	Comment noted. No action required.
	Novartis Pharmaceuticals UK Limited	No comments.	Comment noted. No action required.

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Equality and Diversity	AstraZeneca	AstraZeneca has not identified any issues related to equality that should be covered in the remit or scope of this appraisal. However, please refer to our comment below in Other Considerations.	Comment noted. No action required
	Primary Care Diabetes Society	No impact on protected characteristics	Comment noted. No action required
	The Renal Association (endorsed by Royal College of Physicians)	No comments	Comment noted. No action required
	Novartis Pharmaceuticals UK Limited	No comments.	Comment noted. No action required
Other considerations	AstraZeneca	Use of dapagliflozin in primary care Dapagliflozin is currently available across primary and secondary care treatment settings for patients with T1DM, T2DM and heart failure with reduced ejection fraction (HFrEF). A positive recommendation for dapagliflozin in CKD is expected to extend the benefits of dapagliflozin to all eligible patients with CKD, including patients with CKD who do not have comorbid T2DM. Enabling initiation of dapagliflozin for the treatment of CKD in the primary care setting would ensure consistent equality of access in patients with	Comment noted. The committee will discuss the most appropriate setting for dapagliflozin during the committee meeting. No changes to scope necessary.

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		and without T2DM, without relying on access to specialist care, which currently varies by geography. Subgroups The subgroups suggested within the draft scope are considered to be appropriate; there are no additional subgroups of relevance.	
	Primary Care Diabetes Society	No comments	Comment noted. No action required
	The Renal Association (endorsed by Royal College of Physicians)	It is likely that if approved this intervention will need to be implemented across the whole health care sector with a significant role for primary care. It is therefore important that we are clear about what (if any) monitoring is required before or after introduction of dapagliflozin and how this drug may affect diabetes management in those individuals with both CKD and diabetes.	Comment noted. The committee will discuss the most appropriate setting and recommended monitoring for dapagliflozin during the committee meeting. No changes to scope necessary.
	Novartis Pharmaceuticals UK Limited	No comments.	Comment noted. No action required.
Innovation	AstraZeneca	Yes. Numerous pharmacologic interventions have been investigated for CKD which have had limited success at reducing the risk of progression to ESKD and no significant treatment effects have been reported against all-cause mortality.[14] In the pivotal DAPA-CKD trial, which was stopped early due to overwhelming efficacy, dapagliflozin showed positive treatment effects for the treatment of CKD patients both with and without comorbid T2DM; this is of particular	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its

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		significance as there has not been any new treatment options for CKD patients without comorbid T2DM for over 20 years. Furthermore dapagliflozin is the only treatment for CKD to have demonstrated a statistically significant improvement in all-cause mortality in a renal outcomes trial (HR 0.69 [95% CI, 0.53, 0.88)], p=0.004) compared to standard care.[2] Dapagliflozin is an innovative treatment for patients with CKD with or without T2DM and offers substantial clinical benefit over and above current standard care; an early and sustained treatment benefit compared to current standard care was observed in the DAPA-CKD trial in both the primary composite outcome of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes and a key secondary endpoint of all-cause mortality.[2] Furthermore, therapies currently used to manage and reduce progression of CKD, such as ACE inhibitors and ARBs, require extensive dose titration over a period of many weeks and are associated with a risk of hyperkalaemia and hypotension.[11, 15-18] Unlike ACE inhibitors and ARBs, dapagliflozin is not associated with these complications.	recommendations. No action required.
	Primary Care Diabetes Society	The STA will have significant impact on health outcomes; mortality, morbidity and will be cost effective as there will be delay in people reaching ESRF, ultimately also improving the QOL of the patients. DAPA-CKD trial	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations. No action required.
	The Renal Association	It is our view that the SGLT2i as a class will provide a significant additional benefit to people with chronic kidney disease over and	Comment noted. Where relevant and appropriate, the extent to

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	(endorsed by Royal College of Physicians)	above standard of care. The evidence obtained from large cardiovascular outcome trials, primary renal outcome trials and heart failure trials provides consistent evidence for such a benefit. It needs to be highlighted that the benefits seen across these studies is significantly greater than the benefits that were identified in relation to the use of inhibitors of the renin angiotensin aldosterone system in the late 1990s and early 2000's which were the last significant therapeutic intervention that had been identified to be of benefit to people with CKD.	which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations. No action required.
	Novartis Pharmaceuticals UK Limited	If the use of dapagliflozin for chronic kidney disease is able to reduce the need for kidney replacement therapy, the technology might alleviate the NHS capacity burden relating to dialysis and kidney transplantations. These benefits are unlikely to be included in the QALY calculation.	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations. No action required.
Questions for consultation	AstraZeneca	Comments have been provided above with regards to the population, comparators and outcomes specified in the draft scope, as well as issues related to equality, and the innovativeness of dapagliflozin. Some of these key comments have been re-iterated below. **Which treatments are considered to be established clinical practice in the NHS for chronic kidney disease? How often are steroids and antiplatelet drugs given in this population?**	Comments noted. No action required.

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		ACE inhibitors and ARBs are recommended in patients with a uACR of >70 mg/mmol regardless of underlying comorbidities, and for patients with lower levels of albuminuria who have comorbidities such as hypertension (recommended if uACR is >30 mg/mmol) or diabetes (recommended if uACR is >3 mg/mmol), who can tolerate such treatment. Antiplatelets are recommended for the secondary prevention of CV disease in patients with significant CV disease who have had a CV event in the past. They are not commonly used as primary prevention and are avoided in patients with advanced stages of CKD. AstraZeneca has assumed NICE are referring to statins (rather than steroids), which are recommended for the primary prevention of CV disease in patients who have 10% or greater risk of developing CV disease within the next 10 years or for secondary prevention in patients with established CV disease.[10, 19] Preliminary data analyses from the UK Clinical Practice Research Datalink (CPRD) shows that ACE inhibitors are used by [redacted] of patients, ARBs by [redacted] of patients, statins by [redacted] of patients and antiplatelets by [redacted] of patients around the time of CKD diagnosis.[20] Based on UK clinical input, treatment with ACE inhibitors or ARBs is not universal across all CKD patients, in part due to guideline recommendations and in part due to tolerability issues and challenges with repeat appointments for dose titrations which can be difficult for patients to adhere to.[12]	

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		In clinical practice, would people always be stable on the maximum tolerated dose of ACE inhibitors or ARBs before dapagliflozin would be considered? As discussed above, AstraZeneca has requested that the phrase "who are stable on" is changed to "who are receiving individually optimised standard care" to make clear that the term stable refers to the dose of standard care rather than the disease itself. Overall, AstraZeneca suggests that the answer to this question is no. As discussed above, not all patients who may benefit from treatment with dapagliflozin will receive ACE inhibitor or ARB therapy in clinical practice, due to guideline recommendations or their inability to tolerate these medications. Dapagliflozin may therefore be prescribed in the absence of an ACE inhibitor or ARB when these therapies are not recommended or tolerated. Based on clinical expert input, prescription of dapagliflozin in the absence of background ACE inhibitor or ARB could be relevant especially in CKD patients at risk of hypotension and/or at risk of hyperkalaemia which limits the prescription of an ACE inhibitor or ARB.[12] **In what circumstances would dapagliflozin be added to standard care? Would it ever be used to treat people whose CKD is responding to treatment with standard care?** The concept of "response" is not routinely used to describe CKD treatments. This is because a key goal of CKD treatment is to avoid future events, such as hospitalisation, disease progression and	

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		premature death. As such, it is not possible to measure the "response" at an individual patient level. Instead, the treatment goal in CKD is to reduce disease progression, risk of progression to ESKD, risk of morbidity (including hospitalisation and acute kidney injury) and risk of premature death. Patients receiving individually optimised standard care are still exposed to a significant residual risk of disease progression, morbidity and mortality. Dapagliflozin has demonstrated a significant treatment benefit compared with placebo when added to standard care in the DAPA-CKD study.[2] Therefore, it is anticipated that dapagliflozin will be used as an add-on therapy to standard care, which comprises a variety of individually optimised therapies.[2] **Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom dapagliflozin is expected to be more clinically effective and cost effective or other groups that should be examined separately?** As discussed above, the subgroups suggested are considered appropriate; there are no additional subgroups of relevance. **Where do you consider dapagliflozin will fit into the existing NICE pathway, chronic kidney disease?** Based on clinical expert input, AstraZeneca considers dapagliflozin should be included in the existing NICE pathway as a first-line therapy option in the primary or secondary care setting used upon diagnosis of CKD to prevent progression of CKD. Dapagliflozin would	

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		be considered as a 'co-treatment' alongside current standard care, which may include ACE inhibitors or ARBs in patients for whom ACE inhibitors or ARBs are recommended and can be tolerated.[12] **Do you consider that the use of dapagliflozin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** No, AstraZeneca does not consider the use of dapagliflozin to result in any benefits that cannot be captured in the QALY calculation. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly**. Oral dapagliflozin has been widely used in the NHS, in both primary and secondary care settings, as a treatment for T1DM, T2DM and HFrEF since the recommendations by NICE in 2019, 2013 and 2020 respectively.[21-23] As such, both primary and secondary care clinicians have extensive clinical experience in prescribing dapagliflozin, and therefore we anticipate no barriers to adoption in CKD.	
	Primary Care Diabetes Society	No comments	Comment noted. No action required.
	The Renal Association (endorsed by	Standard of care for people with CKD is as defined in the NICE 2014 guideline. There are subgroups of patients with kidney disease who require immunosuppressive therapy including steroids. Data from SGLT2i renal primary outcome studies excluded patients on	Comment noted. No action required.

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	Royal College of Physicians)	significant dosage of steroids and this needs to be factored into the advice that emerges from this technology appraisal. In relation to standard of care it is important to appreciate that in the real world many people with chronic kidney disease are unable to tolerate maximal dosages of inhibitors of the renin-angiotensin-aldosterone system. Similarly within the individual SGLT2i studies it is important to consider not just whether the patients were on these medications but how many of them were on maximal therapy. Chronic kidney disease is a very slowly developing long-term condition and individuals may lose kidney function over very long periods. It is important to ensure that intervention has started early enough to maximise the chance that that individual is most likely to be protected from the need to commence renal replacement therapy in their lifetime. This needs to be factored into the QALY calculation. People with CKD are not homogenous and include individuals with varying rates of decline in kidney function and varying levels of albuminuria. Current primary renal outcome trials only included people with proteinuria of greater than 25 or 30 ACR. It would be important to clarify risk-benefit balance in those with lesser degrees of proteinuria and earlier kidney function. SGLT2i as a class are now recommended as the preferential treatment for people with diabetes and evidence of early kidney disease with stronger evidence for canagliflozin in individuals with poorer kidney function (GFR,45) where the glycaemic benefit is less but where the cardio renal benefits persist. Dapagliflozin appears to have a similar effectiveness of people with diabetes to that found in the canagliflozin primary outcome study but has extended this to	

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		individuals with lower GFR (down to 25) and albuminuria but more importantly in subgroups without diabetes. Therefore current evidence suggests a need to revise not just the diabetes renal guidelines but CKD guidelines. We do not believe that there are going to be significant barriers to adoption of dapagliflozin in relation to chronic kidney disease. Primary care has been prescribing SGLT2i for many years and are experts in managing this class of drug. It will be important to ensure that there are minimal barriers to prescribing of dapagliflozin. Therefore whilst there will be a need to ensure that the right patient has been given the drug, thereafter monitoring should only be as required by the evidence from the clinical trials.	
	Novartis Pharmaceuticals UK Limited	***How often are steroids and antiplatelet drugs given in this population?*** While we do not have a response to this question, we wanted to highlight that, as per our comment to the background section, we assume that this question is meant to refer to statins rather than steroids. ***In clinical practice, would people always be stable on the maximum tolerated dose of ACE inhibitors or ARBs before dapagliflozin would be considered? In what circumstances would dapagliflozin be added to standard care? Would it ever be used to treat people whose CKD is responding to treatment with standard care? [...] Where do you consider dapagliflozin will fit into the existing NICE pathway, chronic kidney disease?***	Comment noted. No action required.

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		In order to be included in the dapagliflozin DAPA-CKD trial, patients had to be on a stable and maximum tolerated dose of an ACE inhibitor or ARB for at least 4 weeks, if not medically contraindicated. Dapagliflozin (or placebo) was given in addition to an ACE inhibitor or ARB. To be enrolled in the clinical trial, patients also had to have evidence of increased albuminuria for at least 3 months, with a urine albumin creatinine ratio (UACR) ≥200 and ≤5000 mg/g at study visit 1. The trial thus only included patients whose proteinuria persisted despite treatment with a maximum tolerated dose of an ACE inhibitor or ARB. If recommended by NICE as a cost-effective treatment option, we expect that in clinical practice, dapagliflozin will be used in line with the population included in the clinical trial, reflecting the available evidence, i.e. as an add-on therapy if proteinuria persists despite treatment with a maximum tolerated dose of an ACE inhibitor or ARB and if eGFR is between 25 and 75 mL/min/1.73m^2. ***NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process.*** We agree that the STA process is appropriate for this appraisal. *References provided but not included here.*	
Additional comments on the draft scope	AstraZeneca	In relation to the "Related NICE recommendations and NICE Pathways", AstraZeneca requests the following updates: • Dapagliflozin for treating heart failure with reduced ejection fraction [ID1656] is currently listed as a technology appraisal	Comment noted. TA679 (formally ID1656) has been added as a related technology appraisal. The suggested COVID-19 rapid guidelines are

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		in development, however AstraZeneca would like to note that ID1656 has now been published (on 24th February 2021) and so is no longer in development. • AstraZeneca notes that the following COVID-19 Rapid Guidelines are also relevant to this appraisal. These guidelines discuss the need to modify treatment plans to minimise face to face contact during the pandemic, which dapagliflozin could contribute to. ○ COVID-19 rapid guideline: chronic kidney disease [NG176] ○ COVID-19 rapid guideline: dialysis service delivery [NG160] ○ COVID 19 rapid guideline: renal transplantation [NG178]	interim guidance only and therefore have not been added to the scope.
	Primary Care Diabetes Society	No comments	Comment noted. No action required.
	The Renal Association (endorsed by Royal College of Physicians)	No comments	Comment noted. No action required.

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	Novartis Pharmaceuticals UK Limited	No comments	Comment noted. No action required.