NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132) [ID627]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **Merck Sharp & Dohme**
   - **British Hypertension Society**
   - **HEART UK**
   - **British Heart Foundation**
   - **Royal College of Pathologists**

   'No comment' response received from the Department of Health

3. **Comments on the Appraisal Consultation Document from experts:**
   - **Dr A Viljoen** – clinical expert, nominated by Merck Sharp & Dohme UK
   - **Professor Anne-Marie Kelly**– clinical expert, nominated by Royal College of Pathologists

4. **Comments on the Appraisal Consultation Document received through the NICE website**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (review of NICE technology appraisal guidance 132)

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Merck Sharp & Dohme UK Ltd	MSD welcomes the opportunity to comment on the appraisal consultation document (ACD) for ezetimibe. There are particular groups of patients that will be disadvantaged if this preliminary guidance1 is made final, which include: • People with heterozygous familial hypercholesterolaemia (HeFH); • High-risk primary prevention patients, especially those with type 2 diabetes mellitus; • High-risk secondary prevention patients. MSD made a clear clinical and cost-effectiveness case for treating these patient groups with ezetimibe co-administered with a statin, where dose titration of the statin is inappropriate and/or limited by intolerance. If this recommendation becomes final, there would be no other treatment option for these patients given the recommendations in NICE Lipid Modification Clinical Guideline, CG1812. The beliefs and actions by the ERG and Committee regarding the evidence base and economic arguments have led to what we believe is a flawed preliminary recommendation. The following summarises the key issues for each of these patient groups, and these are outlined in more detail in the following pages: • People with HeFH: o failure to consider all the evidence for these patients, including the impact of higher baseline LDL-c levels, which has resulted in a lack of a recommendation for the use of ezetimibe as an add-on to statin in this extremely high-risk patient group. • High-risk primary prevention patients, especially those with type 2 diabetes mellitus: o failure to consider the impact of increasing 10-year cardiovascular	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). Please see Section 4 of the FAD for further details and responses to comments on each issue below.

Consultee	Comment [sic]	Response
	(CV) risk levels above 20% when considering cost-effectiveness. • High-risk secondary prevention patients: ○ While the Committee has accepted the relationship between LDL-c and CV event reduction based on the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis[3] and using this in the cost-effectiveness model for the primary prevention and ezetimibe monotherapy populations, we are concerned by the failure of the Committee to recognise that IMPROVE-IT[4] is consistent with the CTTC meta-analysis; ○ the inappropriate use of the IMPROVE-IT data in the cost-effectiveness model to analyse the impact of using ezetimibe as add-on to statin in this patient group. Finally, we are disappointed that the Committee has not taken into account the future budget impact of ezetimibe, reflecting ezetimibe's impending patent expiry in April 2018.	
Merck Sharp & Dohme UK Ltd	**1. People with Heterozygous Familial Hypercholesterolaemia** We are concerned that all the relevant evidence submitted by MSD with respect to patients with HeFH has not been considered in developing the ACD, which has led to a lack of a recommendation in the add-on to statin population. The scope outlines that people with HeFH are a relevant sub-group and clinical and cost-effectiveness evidence for this sub-group has been provided by MSD (Section 4.8 and Section 5.9.2, Manufacturer's submission[5]). The key summary of the cost-effectiveness estimates from the submission are summarised below, based on extrapolating the base case results to higher baseline LDL-c levels seen in people with HeFH (at least 8 mmol/L)[6,7]. As highlighted by the analysis, the cost-effectiveness of ezetimibe increases at higher baseline LDL-c levels. **Figure 1 Incremental cost-effectiveness ratios (ICERs) for base populations, by varying baseline LDL-c levels -** *The company reproduced figure 41 from the company's submission in its response to consultation and has not been reproduced here. Please see Committee papers for the full response.* While the following is stated on page 45 of the ACD, there is no mention of the cost-effectiveness evidence considered and the conclusion reached by the Committee for the HeFH population with respect to ezetimibe monotherapy or adding-on ezetimibe to statin under section 4 of the ACD ('Considerations of the evidence')[1]: "*The committee was aware of evidence from 4 clinical trials in adults with type 2*	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). This includes people with heterozygous familial hypercholesterolaemia.

Consultee	Comment [sic]	Response
	diabetes, a trial in patients with chronic kidney disease and a trial in patients with heterozygous familial hypercholesterolaemia. The Committee considered the cost-effectiveness estimates for the subgroups presented by the company" and cross-references to section 3.7 and 4.18. The preliminary recommendation in the ACD recommends the restricted use of ezetimibe as monotherapy for patients with non-familial hypercholesterolaemia, as well as in those patients with HeFH using the same criteria. This conclusion is inconsistent with the cost-effectiveness evidence submitted by MSD, which showed by extrapolating the cost-effectiveness estimates to high baseline LDL-c levels, ezetimibe is clearly a cost-effective option for patients with HeFH in both monotherapy when a statin is considered inappropriate or is not tolerated, as well as add-on statin. MSD believes that the cost-effectiveness evidence related to HeFH has not been adequately considered by the Committee in drafting the ACD. The NICE Committee is requested to review all the clinical and cost-effectiveness data and consider the appropriate recommendation for this group at very high-risk of experiencing cardiovascular events.	
Merck Sharp & Dohme UK Ltd	**2. <u>High-risk primary prevention patients, especially those with type 2 diabetes mellitus</u>** Among the primary prevention patients, there are particular cohorts at high-risk of cardiovascular disease, for example, those with high baseline LDL-c levels or patients with co-morbidities such as diabetes. Patients with diabetes, for example, are at two to three times higher risk of cardiovascular events compared to those without diabetes[8]. MSD believes that one of the key factors impacting cost-effectiveness of primary prevention patients has not been fully considered. The ERG has recognised that "*Decreasing the 10-year cardiovascular risk to 10%...*" increased the ICER (section 3.32, ACD[1]), however, they have not identified and recognised that increasing the 10-year CV risk from 20% to 30% also has a significant impact on the ICERs for the primary prevention populations. Scenario analyses evaluating the impact of increasing the 10-year CV risk levels were submitted by the manufacturer in the following sections in the submission[5] with the corresponding ICERs: • Primary prevention, add-on to statin, 30% 10-year CV risk, ICER: £41,783 per QALY (Table 71, page 174) • Primary prevention with diabetes, add-on to statin, 30% 10-year CV	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). This includes people with type 2 diabetes mellitus.

Consultee	Comment [sic]	Response
	Risk, ICER: £22,335 per QALY (Table 83, page 187) There is no evidence in the ACD that the Committee has considered the ICERs for the primary prevention population and the primary prevention sub-group population with type 2 diabetes, when the 10-year CV risk is increased to 30%. As a consequence, MSD believes that key evidence submitted by the manufacturer and the consideration of high-risk patient cohorts, such as the diabetes population, which are cost-effective, has been overlooked in developing the ACD. As such, MSD requests the following: • Firstly, section 3.32 in the ACD is updated to accurately reflect that a decrease **or** an increase in the 10-year CV risk impacts the ICERs. The text should be updated to the following: "*Changing the 10-year cardiovascular risk to 10% or 30%, which increased the ICER to £47, 067 per QALY or decreased the ICER to £21,187 per QALY gained.*" • Secondly, the Committee considers the impact of increasing as well as decreasing the 10-year CV risk on the ICERs for the primary prevention population, including the sub-group with diabetes add-on to statin, as this evidence originally submitted by MSD does not appear to have been adequately considered – omitting the potential consideration of relevant cohorts (e.g. primary prevention with diabetes, add-on to statin with a 30% 10-year cardiovascular risk) that are cost-effective.	
Merck Sharp & Dohme UK Ltd	**3. High-risk secondary prevention patients** MSD is concerned by the belief of the ERG and the Committee that it was more appropriate to use the IMPROVE-IT clinical data to model the 'secondary prevention, add-on to statin' population rather than using the CTTC meta-analysis (section 4.15, ACD[1]). This approach would only be applicable if we were evaluating the benefit of adding on ezetimibe in patients with the same characteristics of those in the IMPROVE-IT trial[4], in particular those who had low baseline LDL-c and had low residual risk of further CV events. This is explained in further detail below. **The IMPROVE-IT study population is a sub-set of the secondary prevention population** IMPROVE-IT[4] put two hypotheses to the test. The first is that lowering LDL-c from an already low to an even lower level is better, with the results demonstrating that the LDL-c hypothesis from CTTC meta-analysis holds for very low levels of cholesterol. The second is that adding another LDL-lowering agent to a statin	Thank you for your comment. After considering the comments received in response to the ACD, the Committee concluded that although results from IMPROVE IT were consistent with the CTTC analysis, the trial population was not representative of the wider population likely to receive ezetimibe to treat hypercholesterolaemia for the secondary prevention of cardiovascular disease (see section 4.5 of the FAD). The Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD).

Consultee	Comment [sic]	Response
	decreases cardiovascular outcomes (which no other non-statin has demonstrated). To do this, the trial was designed so that the statin plus placebo (control) group would achieve 'at goal' LDL-c level (<1.8 mmol/L on average)[9] while the statin plus ezetimibe group, by nature of the additional LDL-c reduction afforded by ezetimibe, would achieve an LDL-c level of about 1.4 mmol/L or less. The study was conducted in a very specific population presenting with stabilised ACS and low pre-treatment baseline LDL-c levels (mean 2.4 mmol/L). Ezetimibe was evaluated to assess the incremental clinical benefit in a well-treated population on statin with a very low LDL-c. Hence the IMPROVE-IT population is a sub-set of the wider secondary prevention add-on to statin population that would typically be treated with ezetimibe in the real world. The IMPROVE-IT population is therefore not reflective of the patients routinely treated with ezetimibe in UK clinical practice, where their baseline LDL-c levels are much higher[10]. **The clinically relevant (and modelled) population** Ezetimibe is currently used in patients that do not achieve sufficient LDL-c lowering on statins, for example, where statin uptitration is limited by intolerance or because of high baseline LDL-c levels; this was the population modelled in the submission. IMPROVE-IT did not examine this population. Therefore in order to model a more clinically relevant population, MSD took the approach of using the LDL-c hypothesis from the CTTC meta-analysis to estimate ezetimibe's treatment benefit in the modelling approach. **The IMPROVE-IT and SHARP studies are consistent with the LDL-c hypothesis from the CTTC meta-analysis** • Figure 2. Plot of the IMPROVE-IT trial data and statin trials for change in LDL-c versus clinical benefit[4]. *The company reproduced figure 4 from the company's submission in its response to consultation and has not been reproduced here. Please see Committee papers for the full response.* The CTTC meta-analysis of all major statin studies (n=169,138) has established a linear relationship between the absolute reduction in LDL-c and the proportional reduction in major vascular events, where a reduction in LDL-c of 1 mmol/L reduces the incidence of major vascular events by 22%[3]. Hence, a 0.5 mmol/L absolute reduction in LDL-c, reduces the incidence of major vascular events by 11%. This well-accepted analysis was used as the basis for the economic model in the original NICE TA132 review in 2007 and has also been accepted by the Committee for modelling the primary prevention and monotherapy populations in this current review, which MSD supports[1, 12].	

Consultee	Comment [sic]	Response
	In the IMPROVE-IT study, the corresponding mean LDL-c levels at year one were 1.42 mmol/L in the ezetimibe/simvastatin group vs. 1.86 mmol/L in the simvastatin group, a difference of 0.43 mmol/L. Extrapolating the clinical benefit to a per mmol/L basis of LDL-c reduction with ezetimibe in IMPROVE-IT, resulted in a Hazard Ratio (HR) of 0.80 (95% CI [0.68; 0.94]), which is consistent with the HR 0.78 (95% CI [0.76; 0.80], p<0.0001) observed with statins in the meta-analysis performed by the CTTC in 2010 (Figure 1)[3]. Furthermore, in the SHARP trial, an average reduction of 0.85 mmol/L yielded a significant 17% reduction in major atherosclerotic events, again similar to the effects seen in the CTTC meta-analysis[12]. As can be seen in Figure 2, the LDL-c/cardiovascular event reduction relationship obtained by ezetimibe in IMPROVE-IT sits on the CTTC line, and therefore is consistent with (and was predicted by) the CTTC meta-analysis[4,13,14]. Thus, demonstrating that a 1 mmol/L reduction in LDL-c with ezetimibe would lead to a 22% reduction in the incidence of major vascular events. MSD is concerned to hear that despite this unequivocal scientific evidence and the support of clinical experts[15], member(s) of the Committee question whether the IMPROVE-IT study was consistent with the CTTC meta-analysis. **It is inappropriate to use the IMPROVE-IT data to analyse the impact of using ezetimibe as add-on to statin in the overall secondary prevention patient population** For patients that have higher baseline LDL-c levels, a higher expected absolute reduction in LDL-c with lipid-lowering therapy is expected, and therefore, based on the CTTC meta-analysis, a larger reduction in the incidence of major cardiovascular events. The relative risk reduction in cardiovascular events observed in the IMPROVE-IT study is representative of an additional mean LDL-c reduction of 0.43 mmol/L with simvastatin and ezetimibe compared to simvastatin alone. The relatively small absolute LDL-c reduction in this study was expected due to the low baseline LDL-c levels, and as highlighted above, is consistent with the LDL-c hypothesis from CTTC meta-analysis. In the target population under consideration for this appraisal, much larger absolute LDL-c reductions are expected as patients are expected to have a higher pre-statin baseline LDL-c level of at least 4.32 mmol/L (Section 5.2, Manufacturer's submission[5]). By applying the expected percentage LDL-c reduction derived from the revised manufacturer's meta-analysis of an additional reduction of 15.6% (95% CI 17.05 to 14.13) to a baseline of 4.32 mmol/L, this results in an expected LDL-c reduction of 0.67 mmol/L. This is much larger than that observed in IMPROVE-IT	

Consultee	Comment [sic]	Response
	due to the higher baseline LDL-c levels of the patients that are currently treated with ezetimibe. As such, the relationship between LDL-c and cardiovascular events from the CTTC meta-analysis was used to extrapolate to this larger absolute LDL-c reduction and derive relevant treatment effect estimates for ezetimibe that were applied in our model. For a 0.67 mmol/L absolute LDL-c reduction, this corresponds to a RR of 0.83 for non-fatal MI and 0.90 for non-fatal stroke. These are much higher than observed in the IMPROVE-IT study because of the larger expected reductions in LDL-c, but are the appropriate estimates for the treatment effect of ezetimibe in a secondary prevention, add-on to statin population with a pre-statin baseline LDL-c of 4.32 mmol/L. Therefore, it is inappropriate to apply the fixed RR from the IMPROVE-IT study to the secondary prevention add-on to statin population in the submission. Furthermore, as highlighted by Figure 1, in our modelling approach based on CTTC meta-analysis relationship, the cost-effectiveness of ezetimibe increases as the baseline LDL-c levels increase, and this is because the expected absolute LDL-c reduction is greater (see Figure 1 and Figure 40, Manufacturer's submission[6]). By using the IMPROVE-IT treatment effect estimates in the economic model for the clinically relevant 'secondary prevention, add-on to statin' population, the benefit associated with ezetimibe is significantly underestimated, thereby overestimating the ICERs. The relationship between LDL-c and cardiovascular outcomes from the CTTC meta-analysis is the only appropriate way to model the cost-effectiveness of the secondary prevention, add-on to statin population, as well as the additional cohorts such as monotherapy and primary prevention. MSD is extremely disappointed by the Committee and the ERG for the inappropriate application of the IMPROVE-IT data in developing the preliminary recommendation, and the negative consequences this will have on patients if these are made final in their current form. The current recommendation would deny patients at the highest risk access to a treatment option that would avoid further cardiovascular events.	
Merck Sharp & Dohme UK Ltd	**4. <u>Use of cholesterol targets in current clinical practice (Section 4.2, ACD)</u>** The Committee has recognised that one of the key changes in the updated NICE Clinical Guideline for Lipid Modification (CG181)[2] published in July 2014 was a greater emphasis on managing cardiovascular risk rather than meeting a specific cholesterol target. However, the Committee has failed to adequately recognise that cholesterol targets are routinely used in clinical practice, and will remain so for the foreseeable future.	Comment noted. Appropriate control of cholesterol concentrations should be based on individual risk assessment in the relevant population (see section 1.7 of the FAD).

Consultee	Comment [sic]	Response
	A large number of patients are still not reaching recommended cholesterol levels. In 2011, the Health Survey for England reported that 60% of men and 38% of women with CVD (the expectation is that the majority had received advice on lifestyle modification and drug treatment where deemed advisable) had TC levels below 5 mmol/L (the NICE CG675 'audit level' for those with CVD, diabetes or hypertension who are on drug treatment), while only 27% and 10% respectively had levels below 4 mmol/L (the then-NICE 'target level' for this high-risk group) in 2011[16]. As evident, there is an opportunity to further reduce the risk of future major cardiovascular events in such patients by further reducing TC and LDL-c with the use of ezetimibe. A recent report from Soran *et al.* has shown that whilst CVD risk is useful in determining treatment, the LDL-c reduction achievable is critical.[17] They showed that pre-treatment LDL-c concentration has a large determining factor on the individual that benefits treatment – those with high pretreatment LDL-c (largest absolute change on treatment) and greatest CVD risk, benefit more from lipid lowering therapy and have lower NNTs (number needed to treat). Lack of LDL-c targets and a focus on CVD risk benefits people with lower pre-treatment LDL-c, whereas people with more marked hypercholesterolaemia benefit more from specific targets. The positioning of ezetimibe and cost-effectiveness estimates should be considered by the Committee in light of the common use of cholesterol targets in clinical practice – and recognising the benefit that can be offered to patients that are not appropriately controlled on the maximum tolerated dose of statin by adding in ezetimibe and further reducing their risk of major CV events. The patients that could benefit most from ezetimibe are those at the highest risk of experiencing cardiovascular events, such as those with existing CVD (secondary prevention), or co-morbidities such as CKD or diabetes.	
Merck Sharp & Dohme UK Ltd	**5. <u>Baseline LDL-c levels is a key factor impacting cost-effectiveness</u>** In section 3.32 of the ACD[1], there is a summary of the key parameters that the ERG has determined had the greatest impact on the ICER. Varying baseline LDL-c levels also has a significant impact on the ICERs and this is not a factor currently listed in this section. For the base case analyses for the primary and secondary prevention populations, and the chronic kidney disease and diabetes sub-groups, the base case assumed a baseline LDL-c pre-statin treatment of 4.32 mmol/L (see section 5.2, Manufacturer's submission[5]). Scenario analyses evaluating the impact of alternative pre-statin LDL-c levels on the cost-effectiveness estimates were submitted by the manufacturer and shown in the following figures in the submission: figures 1, 40, 42 and 49. Figure 1 above, taken from the manufacturer's submission, summarises the impact	Comment noted. Appropriate control of cholesterol concentrations should be based on individual risk assessment in the relevant population (see section 1.7 of the FAD).

Consultee	Comment [sic]	Response
	on the base case populations and the primary prevention with diabetes sub-group. There is no evidence in the ACD that the NICE Committee have considered the impact of altering baseline LDL-c, pre-statin treatment levels on ICERs, where at higher baseline LDL-c levels, the cost-effectiveness of ezetimibe increases. As such, MSD requests the following: - Firstly, section 3.32 in the ACD is updated to add an additional bullet reflecting the significant impact of altering baseline LDL-c levels, for example: "*Changing the baseline LDL-c levels, where at higher baseline LDL-c levels, the cost-effectiveness of ezetimibe increases…*" - Secondly, the NICE Committee considers the impact of altering the baseline LDL-c levels on the ICERs for all the modelled populations.	
Merck Sharp & Dohme UK Ltd	**Direct meta-analysis of clinical outcomes (Section 3.11, ACD)** MSD disagrees with the ERG's view that the manufacturer should have conducted a direct meta-analysis of clinical outcomes as it would provide no relevant information for this appraisal. Ezetimibe has been studied in three CV outcomes trials in three very distinct populations, SEAS[18], SHARP[12] and IMPROVE-IT[4]. Two of these have studied ezetimibe + statin versus placebo, a comparison that is not relevant to this review of TA132 and this has been acknowledged and agreed by the Committee (see section 4.5, ACD[1]). The IMPROVE-IT trial compared ezetimibe + statin versus statin which is relevant to this review, therefore one CV outcomes trial becomes relevant evidence for the populations under review. In 2015, two meta-analyses evaluating ezetimibe's effect on CV outcomes have been published, and both of these reaffirm the view that only three trials have been designed to appropriately evaluate the effect of ezetimibe on CV outcomes[19,20]. MSD believes that this statement from the ERG in section 3.11 of the ACD should be removed as a direct meta-analysis of clinical outcomes, as suggested by the ERG, would provide no relevant information for this appraisal.	Comment noted. This section was removed from the FAD.
Merck Sharp & Dohme UK Ltd	**6. Non-CV Death benefit** The Committee has assumed the following with respect to modelling the treatment effect of ezetimibe for the cost-effectiveness model (section 4.15, ACD): "*It noted the ERG's comment that there was no statistical association between LDL-c and non-cardiovascular related deaths in the CTTC meta-analysis, and concluded it was unreasonable to assume that the treatment effect of ezetimibe should apply to*	Comment noted. This section was removed from the FAD.

Consultee	Comment [sic]	Response
	non-cardiovascular related deaths" While this is consistent with the approach taken in the original TA132 review[21], this differs from the approach taken in the latest Clinical Guideline, CG181[2], published in July 2014 where the most plausible estimates for non-CV death were applied. As part of this guideline, the treatment effect related to statin versus placebo for the add-on to statin analyses was derived from a meta-analysis of RCT data with CV endpoints and used to model the treatment benefit associated with statins in the economic analyses; the same data was applied in our model. The treatment effect estimates of ezetimibe used in our model are derived from the CTTC meta-analysis of 26 RCTs. As such, MSD modelled the non-CV benefit using the most plausible estimates to be consistent with the most recent approach taken by NICE (NICE CG181), and explored the uncertainty associated with this through one-way sensitivity analysis and PSA. By the ERG taking the approach stated in the ACD there is an inconsistency in the approach taken to producing NICE guidance.	
Merck Sharp & Dohme UK Ltd	**7. Ezetimibe's patent expiry in 2018** The patent for ezetimibe expires in two years' time and MSD is disappointed that the Committee has not taken this into account as part of their decision making. As highlighted with the manufacturer's submission, significant price falls are expected upon patent expiry in-line with other lipid-lowering therapies, and the ICERs for ezetimibe fall substantially under the £20,000 per QALY threshold when this is applied in year 3 onwards of the analysis using a conservative 75% price reduction.	Comment noted. Please see section 4.22 of the ACD. The Committee did not consider the any anticipated price fall associated with patent expiry because a specified price has to be available and guaranteed across the NHS (see section 5.5 of the Guide to the methods of technology appraisal 2013).
Merck Sharp & Dohme UK Ltd	**References** *The company submitted several references in its response to consultation and have not been reproduced here. Please see Committee papers for the full response.*	Comment noted. No action required.
Heart UK	HEART UK is the Nation's Cholesterol Charity providing expert support, guidance and education to individuals with raised cholesterol, atherosclerosis and other lipid conditions. To this aim the charity provides high quality literature, a Cholesterol Helpline, a Patient Charter, an extensive website, a range of educational videos, the Ultimate Cholesterol Lowering Plan© and a range of electronic communication tools aimed at increasing the awareness of cholesterol. HEART UK also supports the health care professionals who work and care for patients (and their families) with raised and unhealthy patterns of high cholesterol and other dyslipidaemias. HEART UK hosts a world class annual scientific conference and other networking events for clinicians, researchers, GP's, nurses and dietitians. The charity maintains a health professional membership scheme,	Comment noted. No action required.

Consultee	Comment [sic]	Response
	provides resources and training to health care professionals. In addition the charity campaigns hard to keep cholesterol and cardiovascular disease at the top of the political agenda and to help ensure better identification, diagnosis and treatment of patients with the aim of preventing deaths from early and avoidable cardiovascular disease. HEART UK works directly with lipid experts in lipid clinics and specialist GP services where the diagnosis, treatment and the on-going management of complex lipid conditions such as Familial Hypercholesterolaemia (FH) Familial Combined Hyperlipidaemia (FCH), Type 3 Hyperlipidaemia and Lipoprotein Lipase Deficiency (LPLD) take place. In addition these centres support people with complex secondary dyslipidaeamias, secondary to and alongside other co-morbidities. Lipid clinics also support patients that have suspected statin intolerance; the aim being to identify a level of treatment and lifestyle advice that provides some protection but with minimal side effects. The majority of individuals diagnosed with a primary dyslipidaemia will require lifelong treatment with cholesterol lowering medication in order to reduce their chances of early and avoidable death from coronary heart disease. These patients are often highly motivated to make changes to their diet and lifestyle and to maintain regular medication. Recent successes in generating awareness of the dangers of high cholesterol and in identifying individuals with raised cholesterol have resulted in an increase popularity of the Cholesterol Helpline, and the charities website and social media networks resulting in the need for extra resource to support these communications especially the helpline. HEART UK wishes to let it be known of our overall disappointment with this initial recommendation, which leaves a significant number of patients at a disadvantage.	
Heart UK	In this letter of response I wish to detail the concerns of HEART UK: 1. (4.21) The main problem in this ACD is the lack of mention of familial hypercholesterolaemia - the most significant use of Ezetimibe and recommended in CG71 and a formal comment on continued use in FH needs to be included. In FH the population attributable to risk due to LDL-C is greater than in the general	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). This includes people with

Consultee	Comment [sic]	Response
	population being 50-70% rather than 30-50%- see clinical expert comments for CG71 and the appraisal of Evolocumab. The recent TA on Evolocumab was able to determine the health economics in FH using a multiplier applied to the basic CVD event model of x7 (Benn et al) with sensitivity down to x 3.5. This should be viewed in parallel with this ACD to allow consistency across lipid interventions. In addition, an intervention with formal outcomes evidence for add-on prescription to a statin (Ezetimbe in IMPROVE-IT) and considerable clinical safety data following from many years of prescribing should be preferred to a novel agent with greater efficacy on a surrogate outcome (LDL-C) but no long term safety or efficacy data.	familial hypercholesterolaemia.
Heart UK	2. (4.17) The recommendation of not using Ezetimibe in secondary prevention (established CVD) as an add-on to statins are at odds with clinical evidence and current clinical practice for management of patients with raised LDL-C post statin therapy. The model assumes a uniform risk for a secondary prevention whereas the reality is that this population includes multiple sub-groups with higher event rates - patients with acute coronary syndromes (for event rates see REACH registry -50% excess compared to stable coronary artery disease- as used in Evolocumab TA; and also the exact trial population investigated in IMPROVE-IT); type 2 diabetes with established stable CVD - a common clinical group (see Robinson JG & Stone N; Am J Cardiol 2006; 98: 1405 for NNT vs LDL-C risk curve for different sub-groups) ; as well as a population with lower event rate (chronic stable angina) but high propensity to undergo percutaneous coronary intervention for symptomatic coronary artery disease. Thus angina needs to be included in the model allied with modelling the reduction in need for PCI which in CTT exceeds that for non-fatal MI and is approximately 50% over a 5 year horizon. A scenario analysis for different post-statin treatment LDL-C concentrations in these groups would be interesting and clinically relevant. The Lipid Modification guideline CG67 made a distinction between acute coronary syndromes and stable CVD based on event rates (e.g REACH regsitry) and found higher dose high efficacy on-patent statins cost-effective. In CG181 high efficacy statin costs had reduced so treatment of both ACS and general chronic CVD was cost-effective using highest dose statin therapy. The health economic analyses by Ara (Ara R et al; Eur J Prev Cardiol 2012; 19; 474 & Exp Rev Pharmaecon Outcome Res 2009; 9 : 423) are interesting analogies (with added scenario models) to the current decision problem as the efficacy of Ezetimibe is similar to titration from low	Comment noted. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). Appropriate control of cholesterol concentrations should be based on individual risk assessment in the relevant population (recommendation 1.7 in the FAD).

Consultee	Comment [sic]	Response
	dose generic to high dose high efficacy on-patent statin (16-20% added LDL-C reduction; £26 per month excess costs). It found high-cost statins to be cost-effective in ACS- as did CG67. The data for the Ezetimibe model for secondary prevention (in the higher high ACS sub-group) should be similar and thus scenario B is probably overly conservative and scenario A (with modifications) likely closer to the real world.	
Heart UK	3. As stated in CG181 patients with CKD3+ are at very risk for CVD events. The use of high dose high efficacy statin in CKD3+ is limited by the excess drug toxicity of statins in this patient group. In addition the large and well conducted SHARP trial provides an evidence base for a 17% CVD event reduction in this patient group where statin monotherapy had been ineffective (Wanner C et al; Atorvastatin 20mg in 4D trial in CKD5; NEJM 2005; 353: 238; Fellstrom R et al AURORA Rosuvastatin 20mg in CKD3-4; NEJM 2009; 360: 1395) despite significant LDL-C reductions. Ezetimibe should be recommended for management of CVD risk in patients with CKD3+ given the trial evidence and as a non-lipid associated benefit of combination statin-Ezetimibe therapy cannot be completely excluded.	Comment noted. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). This includes people with CKD.
Heart UK	On a final note; 4. (4.9) The SEAS trial (of combined Simvastatin 20mg & Ezetimibe 10 mg) had a complex primary combined endpoint comprising both valve and CVD outcomes. The prespecified secondary analysis of CVD outcomes alone (underpowered) showed a 22% reduction in events. NICE have disadvantaged patients with heterozygous familial hypercholesterolaemia because the baseline risk has been taken as the same as the general primary prevention population with equivalent LDL cholesterol, whereas it is much higher due to lifelong exposure to high cholesterol. Consequently, the advice not to use risk calculation algorithms has been abandoned: possibly inadvertently. The benefit of statins are related to the absolute LDL lowering and the pretreatment risk, thus a 50% reduction in LDL cholesterol will leave patients with higher LDL cholesterol compared with non-familial hypercholesterolaemia. The modelling would better include notional targets of LDL cholesterol achieved by a 50% reduction. The current modelling based on the existing economic model has led to advice which may not be correct in that Ezetimibe can only be added to statin for secondary prevention in the familial hypercholesterolaemia population. Statin intolerance is one situation where Ezetimibe monotherapy has been found to be cost effective, likely	Comment noted. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). This includes people with familial hypercholesterolaemia.

Consultee	Comment [sic]	Response
	based on the higher pre-treatment LDL cholesterol compared with patients on statins where the absolute extra LDL cholesterol lowering would be smaller. Patients with familial hypercholesterolaemia may well be left with an LDL cholesterol of 4, 5, or 6 mmol/L higher on maximum statin treatment. The recommendation indicates that Ezetimibe might be considered in patients who are intolerant of statins but statin intolerance is not defined and there is a risk that patients will be started on Ezetimibe rather than exploring all statin based options. This would be neither clinically nor cost effective. The way that the modelling has used post-statin LDL cholesterol in addition to underestimation of the baseline risk in familial hypercholesterolaemia both disadvantage this high risk patient group. I hope you find these comments useful and that NICE re-considers its recommendations in light of these, offering access to a greater number of patients that will benefit from Ezetimibe and not disadvantaging a significant high risk patient group.	
British Hypertension Society	The BHS welcomes NICE guidance on the use of ezetimibe following publication of the IMPROVE-IT trial, in the New England Journal of Medicine in 2015. The IMPROVE-IT trial showed the expected benefit of a 23% reduction in LDL cholesterol, from 1.8mmol/L vs. 1.39mmol/L, by adding ezetimibe 10 mg to a statin. The IMPROVE-IT trial studied patients already at low cholesterol levels, following the trial design. At such low levels of cholesterol the many meta-analyses of LDL lowering v outcome from the major statin trials predict about an 8% benefit in relative risk reduction of major cardiovascular events (e.g., CTTC Lancet 2010; 376:1670-81, LaRosa JC et al. N Engl J Med 2005;352). This was achieved in the IMPROVE-IT trial (e.g., 10% reduction in cardiovascular death, non-fatal MI and non-fatal stroke). Thus the premise of the NICE 2007 TA132 Ezetimibe guidance, that the benefit of ezetimibe was related, like statins, to the degree of LDL lowering, has been proven to be correct. However, a survey among BHS members has shown that prescribing of Ezetimibe in usual practice is to achieve, in secondary prevention, a target cholesterol for an individual already on a statin but not at target. For example, select an individual on maximal tolerated statin with an achieved cholesterol of 5.2 mmol/l. Adding ezetimibe typically reduces cholesterol from 5.2 to about 4.2 mmol/l. This reduces CV risk by 22%.	Thank you for your comment. After considering the comments received in response to the ACD, the Committee concluded that although results from IMPROVE IT were consistent with the CTTC analysis, the trial population was not representative of the wider population likely to receive ezetimibe to treat hypercholesterolaemia for the secondary prevention of cardiovascular disease (see section 4.5 of the FAD). The Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD).

Consultee	Comment [sic]	Response
	Calculations of QALYs and ICERs depend on the cost to achieve meaningful risk reduction. In the UK, ezetimibe is not used as it was in the IMPROVE-IT trial to reduce an already low LDL cholesterol to an even lower degree. This is not cost-effective. But to reduce risk by 22%, for the QALY costs shown in NICE TA132 (typically the practice in the UK) is in our view reasonable use of healthcare resources, for those individuals remaining at high CV risk despite optimal use of statins. Calculating QALYs on an 8% relative risk reduction makes ezetimibe uneconomic. But this is not how ezetimibe is used in clinical practice in the UK. Moreover, the patent on Ezetimibe expires in 2018. Calculations for cost per QALY and for ICERs often use a 5 or 10 year prediction. In 2018 generic Ezetimibe will likely be relatively inexpensive, so 10 year calculations of cost should take this into account. In summary, the BHS believes that the current use of Ezetimibe in the UK is correct, used mostly to achieve target cholesterols for individuals in secondary prevention already optimally treated with statin. We believe that the cost calculations in NICE TA132 are correct, and the benefits from Ezetimibe in the IMPROVE-IT trial were as predicted by the CTTC and other meta-analyses. With regard to ezetimibe monotherapy for statin-intolerant patients, the BHS is less secure. But in the absence of data for any other drug ezetimibe at least has good safety data, with cholesterol-lowering ability, so the BHS offers no specific other recommendation.	
Royal College of Pathologists	The Royal College of Pathologists would like to thank you for the opportunity to comment on the Appraisal Consultation Document of this technology appraisal. **General Comments** This document lacks the clinical perspective of the original document having dispensed with the introductory section describing the context in which the technology is used and omitting the entire Section 2 from the previous version which covered “Clinical Need & Practice”. These sections in the previous document included definitions of intolerance to initial statin therapy (2007 1.6) and Hypercholesterolaemia (2007 2.1). Inclusion of these definitions is essential as they are a basis for clinical recommendations and the	Thank you for your comment. The “Clinical need & Practice” section is only provided as part of the ACD or FAD for multiple technology appraisals (like TA132; the original guidance) and not single technology appraisals (like the current appraisal). After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). Recommendation 1.6 gives a definition of

Consultee	Comment [sic]	Response
	guidance cannot be properly interpreted or implemented without them. Overall the document is poorly structured in comparison to the 2007 document and it would be preferable if the revised document followed the original structure and major section headings.	intolerance to statins.
Royal College of Pathologists	**Specific Comments** **1. Preliminary Recommendations** 1.1 The recommendation conflicts with both CG71 and CG81 and recommending that primary heterozygous familiar hypercholesterolemia patients are assessed using the QRISK2 risk assessment tool. In CG81, patients with familial hypercholesterolemia, chronic kidney disease (CKD3+) and type 1 diabetes are specifically excluded from QRISK2 risk assessment. The stated definition of patients eligible for Ezetimibe requiring lipid modification for primary prevention is those having both type 2 diabetes and a risk greater than 20%. CG181 recommends risk assessment in type 2 diabetes patients using the QRISK2 risk tool, it makes no sense to restrict consideration of this technology only to those patients above 20% who have type 2 diabetes as these are at no greater risk than other patients at greater than 20% cardiovascular risk. There is no evidence that the technology has superior efficacy in primary prevention in type 2 diabetes patients. Choice of risk threshold of 20% or greater 10 year risk appears to be an arbitrary decision. In CG181 a 10 year cardiovascular risk of 15% was to found to be the threshold at which statin therapy was cost saving for the NHS and it would have been appropriate to have assessed 15% risk level regardless of diabetes status as part of the assessment. For secondary prevention Ezetimibe was only recommended for those in whom a statin is inappropriate and not tolerated and those patients who are able to tolerate only small dosages of statins insufficient to achieve satisfactory reduction of LDL or non HDL cholesterol does were not considered. In the 2007 version Ezetimibe therapy was recommended as an option treatment for those in whom LDL cholesterol as not appropriately controlled because dose titration is limited by intolerance to initial statin therapy (Section 1.3 2007). This recommendation is particularly relevant and important in patients with familial hypercholesterolemia in whom CG71	Comment noted. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). Appropriate control of cholesterol concentrations should be based on individual risk assessment in the relevant population (recommendation 1.7 in the FAD).

Consultee	Comment [sic]	Response
	recommends achievement of greater than 50% reduction LDL cholesterol and in whom Ezetimibe required to achieve satisfactory control. In CG181 satisfactory of non HDL cholesterol is defined as achievement of greater that 40% reduction in non HDL cholesterol, equivalent to high intensity statin therapy, but this is non referred to anywhere in the document. As the Ezetimibe reduces HDL and non HDL by 15 – 20% the risk reduction will of course be dependent on the pre-treatment non HDL or LDL cholesterol or in statin treated, patients the non HDL or LDL cholesterol achieved after statin treatment. Those with higher non HDL and LDL cholesterol will have greater absolute benefit, and this should be taken into account cost effectiveness analysis. The previous document used baseline pre-treatment LDL cholesterol of 3.5 mmol/L as a basis of the modelling, but a sensitivity analysis with values above and below this could have been included. As some patients have a better response that others, this sensitivity analysis could inform decisions as to whether or not to persist with therapy after initial review of response.	
Royal College of Pathologists	**2. Section 2: The Technology** Section 2 (Section 3 in the original 2007 version) which includes description of the licence indication (Section 2.2) longer refers the use of Ezetimibe in people with homozygous sitosterolaemia and in combination with statin in people with homozygous familial hypercholesterolemia. Although these latter indications may not be covered by this appraisal this should be referred to as previously under the description of licence indications. **3. Section 3** In the previous document section 3 was entitled Evidence and Interpretation which is much more appropriate.	Comment noted. The technology section outlines only the indications with marketing authorisation which are relevant to the final NICE scope for the technology appraisal. The header for section 3 has been changed to “The evidence” in the FAD, which is the designated style for a single technology appraisal like this review. ‘Evidence and interpretation’ is used in multiple technology appraisals, such as the original guidance (TA132).
Royal College of Pathologists	**Section 4** As a recommended in CG 181 assessment of cardiovascular risk of primary invention using QRISK2 should not be applied to patients with chronic kidney disease familial hypercholesterolemia or type 1 diabetes, it does not make sense to discriminate between patients with or without type 2 diabetes who	Comment noted. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). This

Consultee	Comment [sic]	Response
	are at similar cardiovascular risk. Cardiovascular risk thresholds of 10% and 15% should have been modelled demonstrate appropriateness of selection 20% cardiovascular risk rather than altering selection based on the initial analysis of ERG. In Section 4.17 the recommendation against using Ezetimibe as a second line therapy in secondary prevention conflicts with clinical evidence and current clinical practice as many patients fail to achieve satisfactory control of LDL/non HDL cholesterol (defined as greater than 40% reduction of non HDL cholesterol, equivalent of high intensity statin therapy). Patients with established cardiovascular disease with acute coronary syndrome are at higher risk than those with stable coronary disease and should have been considered as separate sub group. As stated in CG71 and CG18, patients with CKD are very high risk of cardiovascular disease and are also susceptible to statin related muscle and renal toxicity. There is extensive safety and efficacy data for Ezetimibe in this group of patients and they are excluded from risk assessment with QRISK2 they should have been specified as a sub group and that could be offered ezetimibe alone or in combination with low dose statins. In patients with familial hypercholesterolemia Ezetimibe in combination with highest tolerated statin dosage represents current standard of care in those patients failing to achieve satisfactory control of LDL-C (defined in CG71 as is greater than 50% reduction of LDL cholesterol). The only available alternative treatments are LDL apheresis (recommended for those with aggressive coronary artery disease in CGG71). These groups should be acknowledged in the guideline and referred to recommendations in CG71 which is soon to be revised. Overall, this guidance falls well short of standards we have come to expect from NICE Technology appraisals and extensive revision be required before this can be implemented clinical practice.	includes people with familial hypercholesterolaemia. Appropriate control of cholesterol concentrations should be based on individual risk assessment in the relevant population (recommendation 1.7).
British Heart Foundation	So far as we are aware, all the relevant evidence has been taken into account, and the provisional recommendations are a sound and suitable basis for guidance. We note the use of the 20%, 10 year CVD risk as the threshold for treatment, and think this will require careful communication to clinicians in the field. We are not aware of any aspects of the recommendations that need particular consideration to ensure unlawful discrimination is avoided, although we note the absence of any advice	Thank you for your comment. Appropriate control of cholesterol concentrations should be based on individual risk assessment in the relevant population (recommendation 1.7).

Consultee	Comment [sic]	Response
	regarding the use of ezetimibe in pregnant women.	

A “no comment” response was received from the Department of Health.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Dr Adie Viljoen clinical expert, nominated by Merck Sharp & Dohme UK Ltd	Thank you for the opportunity to respond. I would like to make three main points: 1. Familial Hypercholesterolaemia (FH) was not mentioned in the draft document and the use of Ezetimibe in this population is not supported by the draft document. The majority of patients with FH are treated with statin together with Ezetimibe. Please note that this group cannot be placed in the primary prevention category. I tried to make this clear at the time of our meeting. CG71 refers to the place of Ezetimibe in treating this population. The recommendation for a 50% reduction of LDL-cholesterol and this document should be aligned such that the CG71 guidelines and QS41 (please see appendix below) are not incongruent. This is not routinely possible with statin monotherapy I propose including the use of Ezetimibe in combination with statin therapy or in monotherapy (in statin intolerant patients) as an option for patients with FH.	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). This includes people with heterozygous familial hypercholesterolaemia. Appropriate control of cholesterol concentrations should be based on individual risk assessment in the relevant population (recommendation 1.7).
Dr Adie Viljoen clinical expert, nominated by Merck Sharp & Dohme UK Ltd	2. The use of CTT data for modelling purposes uses the best available data and this clearly shows the benefit of LDL-cholesterol reduction by statins which is similarly confirmed by the IMPROVE-IT trail data. The fact that the IMPROVE-IT trail falls on the CTT line confirms the LDL-cholesterol hypothesis and depicted by the IMPROVE-IT paper (see figure 1 below). Our understanding of LDL-cholesterol and the fundamental role it plays in the atherosclerosis process as well as the fact that intervention by reducing it is beneficial, is now stronger than ever before. I propose the extrapolation of the LDL-cholesterol data.	After considering the comments received in response to the ACD, the Committee concluded that although results from IMPROVE IT were consistent with the CTTC analysis, the trial population was not representative of the wider population likely to receive ezetimibe to treat hypercholesterolaemia for the secondary prevention of cardiovascular disease (see section 4.5 of the FAD). The Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD).

Nominating organisation	Comment [sic]	Response
Dr Adie Viljoen clinical expert, nominated by Merck Sharp & Dohme UK Ltd	3. Importantly high risk patients for secondary prevention (e.g. patients a history of Acute Coronary Syndrome [ACS]) will only receive a statin and no additional treatment if this draft is not changed to incorporate the treatment of high risk group with a stain plus Ezetimibe (as suggested in TA132). This will lead to substantial under-treatment thus exposing these high risk patients to unjustifiable excess cardiovascular risk. Furthermore even higher risk patients won't receive any additional treatment either (e.g. patients with ACS plus diabetes or patients with two events). I propose the use of statin plus Ezetimibe in secondary prevention if the LDL-cholesterol is at a level where this is deemed cost-effective. Importantly, it was shown to be beneficial (i.e. reduce the composite endpoint) when the LDL-cholesterol reduced from 1.8 to 1.35 mmol/l by the addition of Ezetimibe in the post ASC population (IMPROVE-IT study).	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). This includes people at high risk of cardiovascular events.
Dr Adie Viljoen clinical expert, nominated by Merck Sharp & Dohme UK Ltd	**Appendix** *The clinical expert reproduced figures 4 and 40 from the company's submission, and recommendations 1.3.1.3, 1.3.1.4, 1.3.1.8 to 1.3.1.10 from technology appraisal 132 in its response to consultation and has not been reproduced here. Please see Committee papers for the full response.*	Comment noted. No action required.
Prof Anne-Marie Kelly, clinical expert nominated by the Royal College of Pathologists	I have considered the Appraisal Committee's key conclusions on the use of ezetimibe in for treating primary heterozygous-familial and non-familial hypercholesterolaemia. I understand that the decision to recommend ezetimibe monotherapy for primary prevention who have both type 2 diabetes mellitus and a 20% or greater 10 year cardiovascular risk based on QALY gained. However clinically it is going to be difficult to manage patients without type 2 diabetes who have a high CV risk (20% or higher) and who are intolerant of statins. Currently these patients are offered ezetimibe. Without ezetimibe the therapeutic options for these patients are limited and include fibrates (with limited clinical evidence of effectiveness in terms of CV risk reduction) and nicotinic acid and its derivatives (which are poorly tolerated).	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). Appropriate control of cholesterol concentrations should be based on individual risk assessment in the relevant population (recommendation 1.7 in the FAD). The recommendations do not differentiate treating primary hypercholesterolaemia between primary and secondary prevention of cardiovascular events.

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Patient		I am a 69 year old lady with hypercholesterolaemia who has taken Ezetimibe over an extended period. I had a lot of difficulty from July 2014 until September 2015 trying to get Ezetimibe represcribed as the local CCG, for the Coventry GP practice I attend, was unwilling to let me go back on it despite me being intolerant of statins. I had had a long history of taking it almost since its introduction and it was effective. During the period from August 2013 to early 2014 after I stopped taking it my total cholesterol rose to over 8mmol/L and as I have a high level of Lp"a" - 130-150mgm/dL and am a heterozygote for Factor V Leiden, the lipid clinic I attend is keen for me to keep my LDLC as low as possible. I had a pulmonary embolism in March 2014 and the lipid clinic recommended I go back on the Ezetimibe to reduce the risk of any reoccurrence. It took until September this year to get it prescribed again and within 6 weeks my TC reduced from 7.6 to 5.4mmol/L with HDLC staying the same at 2.5mmol/L. (see attached graphs). This is over a 40% reduction in LDLC in a short time. Although my risk for cardiac events looking at Cholesterol and TG levels alone is not excessively high with a TC/HDLC usually well under 4 at its worst, when taken with the Lp"a" and Factor V Leiden, the lipid clinic thinks the normal way of evaluating risk underestimates my risk. The rapid response to Ezetimibe must indicate that I'm a cholesterol over-absorber rather than an overproducer however, the general prescribing of cholesterol lowering drugs, as far as I know, doesn't distinguish and testing isn't specific. If I look on-line there seem to be numerous CCG's who are very reluctant to allow prescribing of Ezetimibe and this concerns me. How many other patients are out there who might benefit, if it does translate into a reduction of cardiac events. It was mentioned to me that it is becoming clearer that those patients with a high TC but also high HDLC and low TGs don't do well on statins, but I don't know whether there have been any trials done	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has primary heterozygous-familial or non-familial hypercholesterolaemia and the doctor responsible for their care thinks that ezetimibe is the right treatment, it should be available for use, in line with NICE's recommendations. Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. Please see section 5 of the FAD for further details on implementation.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
		yet that show that.	
Health professional (within NHS)	section 3	I'm astonished by the provisional recommendations made. It is absolutely clear from the literature that LDL reduction is the driver behind CV risk reduction. Therefore the baseline level of LDL is a key determinant of the level of CV risk reduction from ezetimibe. It is obsurd to me to base QALY calculation on the absolute reduction of LDL just from the IMPROVE-IT study, as this was a study confined to patients already with low cholesterol levels (hence the reason why it was so hard to recruit patients to in the UK!). It would seem negligent of me as a clinician to withold this drug to someone who was at high risk - if they were either limited in statin dose due to side effects and still had high LDL, or with co-morbiditiies that mean statin treatment alone leaves them at risk of CV events. Furthermore, why havent you discussed the fact that the drug is off patent very soon - thereby rendering the cost analysis at that point irrelevant?	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). The Committee did not consider the any anticipated price fall associated with patent expiry because a specified price has to be available and guaranteed across the NHS (see section 5.5 of the Guide to the methods of technology appraisal 2013).

Role*	Section	Comment [sic]	Response
Health professional (within NHS)		A significant number of patients with FH have problems with statins. There needs to be an alternative - and the cost of ezetimibe is far less than Questran which would be the treatment given if ezetimibe is made unavailable. It is also very relevant that the patent for ezetimibe expires soon. The comments by the committee about the failure to carry out ezetimibe monotherapy vs placebo testing seem to disregard the ethics position that once 4S and other similar studies proved that cholesterol lowering was beneficial, it became impossible to ethically use a placebo group. Therefore, it it wrong to criticise the company for failure to provide this type of evidence. The only reasonable evidence that can be provided is therefore add-on data and the effectiveness of monotherapy has to be imputed from the LDL reduction vs CHD rate data. The reduction achieved by ezetimibe is noted to be only 0.43 mmol/L. However, this is an average figure achieved in a trial and on average half of a group will do better than the average. In the real world (as opposed to trial-land) when we add a drug on, we test to ensure that it is being effective - and therefore if it only adds a tiny amount of extra reduction we stop using it. Thus, for the patients I use ezetimibe in conjunction with a statin I would stop using ezetimibe if I only got a 0.4mmol improvement - On average I would expect more than 1 mmol to be what I see as the benefit from ezetimibe in patients on combination therapy. The LDL : disease risk regression line shows that this adds significant benefit.	Thank you for your comment. After considering the comments received in response to the ACD, the Committee concluded that although results from IMPROVE IT were consistent with the CTTC analysis, the trial population was not representative of the wider population likely to receive ezetimibe to treat hypercholesterolaemia for the secondary prevention of cardiovascular disease (see section 4.5 of the FAD). The Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). The Committee did not consider the any anticipated price fall associated with patent expiry because a specified price has to be available and guaranteed across the NHS (see section 5.5 of the Guide to the methods of technology appraisal 2013).

Role*	Section	Comment [sic]	Response
Health professional (within NHS)		I support the recommendation that Ezetimibe monotherapy should be an option for treating primary heterozygous-familial (FH) and non-familial hypercholesterolaemia in adults with type 2 diabetes and >=20% 10 yr CVD risk or in secondary prevention. However this excludes a specific group in whom such Ezetimibe monotherapy may be required, ie primary prevention in FH. In FH patients it is not appropriate to calculate their CVD risk and they are recognised as justifying cholesterol lowering on the basis of their significantly elevated LDLC level, in line with NICE CG71 and NICE FH pathway. These patients start off with a much higher cholesterol level than other primary prevention patients and, where statins are considered inappropriate or not tolerated, Ezetimibe at present would be the best option to consider, with some patients achieving large reductions (it should be noted that the variability in cholesterol response to Ezetimibe is wider than to an individual dose/brand of statin. The reduction quoted in metanalysis of approx. 20% in LDLC is the average; some patients will have a significantly bigger reduction, others smaller, and this can and should be assessed by measurement after the first month of treatment). I do not support the total non-recommendation for use of Ezetimibe as an add on to statin therapy. The first group of patients in whom add on treatment may be required is heterozygous FH, in line with NICE guidance (as above). With much higher LDLC than in IMPROVE-IT, the ICERs will be considerably less than modelled. Particular attention also needs to be given to very high risk patients, for example those with vascular disease plus diabetes, who are at much higher risk and with higher cholesterol levels, despite maximally tolerated statin, than those in IMPROVE-IT; ICERs will again be less than those calculated. I was disappointed to read that Ezetimibe was no longer regarded as being innovative or a step change in management. Although some new treatments for lowering cholesterol have recently become available, and others are likely to appear over the next few years, these will, or are likely to be, significantly more expensive than Ezetimibe. At the current time statins remain the mainstay of treatment for the vast majority of patients. In those who cannot tolerate any or sufficient statin or in whom LDLC remains high on maximum statin eg in FH, Ezetimibe remains a stepâ€“ change in management for some of these needy patients.	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the available evidence, the Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). This includes people with heterozygous familial hypercholesterolaemia.

Role*	Section	Comment [sic]	Response
Non-profit organisation representing scientists and clinicians		It is not clear to us how the possible role of ezetimibe in the treatment of ACS (and high risk people) was addressed. It appears calculations were made by taking in account the absolute risk reduction demonstrated in the IMPROVE IT. We believe that this, although based on the published data, is not the population of patients to be most likely treated with ezetimibe. We suggest to extrapolate the benefit to those patients with high LDL-cholesterol on the maximal tolerated dose of a statin. In these patients the absolute benefit will be much larger, which is likely to make the intervention much more effective, both in risk reduction and, as a consequence, in NNT. Laufs et al. published a very crude approach which may make more understandable our concerns.[Understanding IMPROVE-IT and the cardinal role of LDL-C lowering in CVD prevention. Laufs U, Descamps OS, Catapano AL, Packard CJ.; Eur Heart J. 2014 Aug 7;35(30):1996-2000. doi: 10.1093/eurheartj/ehu228. Epub 2014 Jun 10.] Patients with genetically elevated cholesterol (FH) and with high LDL in spite of statin treatment will benefit, and you can probably model the system to find a possible LDL-cholesterol threshold at which the benefit is also financially viable.	Thank you for your comment. After considering the comments received in response to the ACD, the Committee concluded that although results from IMPROVE IT were consistent with the CTTC analysis, the trial population was not representative of the wider population likely to receive ezetimibe to treat hypercholesterolaemia for the secondary prevention of cardiovascular disease (see section 4.5 of the FAD). The Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). This includes people with heterozygous familial hypercholesterolaemia and people at high risk of hypercholesterolaemia.
Health professional (within NHS)		We welcome the opportunity to respond to the appraisal consultation document for ezetimibe. We believe that the committee has failed to recognise that in routine clinical use, ezetimibe is added in given to patients with a much higher LDL cholesterol than that in the trials. The reduction of LDL in the trials is noted to be only 0.43 mmol/L, but this is an average figure in the IMPROVE-IT trial for reduction of LDL cholesterol in patients starting with already low LDL cholesterol. As this is an average figure, half of patients would achieve a reduction greater than this. It should also be noted that in routine clinical practice, when using ezetimibe in combination with a statin, the reduction in LDL cholesterol is usually observed to be approximately 1 mmol/L on average, which is much greater than the 0.43 mmol/L quoted. The IMPROVE IT therapeutic scenario is far removed from day to day clinical practice, where ezetimibe is prescribed to patients with high LDL cholesterol that cannot be controlled with statin monotherapy. The "lower	Thank you for your comment. After considering the comments received in response to the ACD, the Committee concluded that although results from IMPROVE IT were consistent with the CTTC analysis, the trial population was not representative of the wider population likely to receive ezetimibe to treat hypercholesterolaemia for the secondary prevention of cardiovascular disease (see section 4.5 of the FAD). The Committee concluded that the recommendations from the original NICE technology appraisal guidance on ezetimibe were still appropriate (see section 1 of the FAD). The Committee was unable to consider international guidance on ezetimibe as evidence. Please see section 3.3 of the Guide to Methods of

Role*	Section	Comment [sic]	Response
		is better" LDL cholesterol regression line shows that this adds significant benefit. Therefore, when interpreting the clinical benefit of ezetimibe, it is important to remember that the absolute risk reduction for the same relative LDL cholesterol lowering diminishes for the same relative LDL cholesterol lowering with lower baseline LDL cholesterol. (1) (See figure in paper) We believe it is therefore incorrect to base QALY calculations on the absolute reduction of LDL cholesterol from the IMPROVE IT trial data. 1 Understanding IMPROVE IT and the cardinal role for LDL-C lowering in CVD prevention, Laufs et al. EHJ 2015 We would also like to draw to the committee's attention to the American College of Cardiology / American Heart Association 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk: a new paradigm supported by more evidence, and the European Society of Cardiology 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. (2,3) These guidelines are evidence based and both recommend the wider use of ezetimibe than NICE are suggesting. They both state that ezetimibe, when added to statin therapy, haves a role in cholesterol lowering and provides clinical benefit. 2. The 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk: a new paradigm supported by more evidence. Robinson JG, Stone NJ. EHJ 2015 3. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. EHJ 2015 The committee has also commented on the fact that there is a lack of evidence comparing ezetimibe monotherapy to placebo. This would not be possible to perform as it would be unethical to do this study; the 4S and other similar studies proved that cholesterol lowering is beneficial, and therefore it is impossible to use a placebo group ethically. Therefore, it is wrong to criticise the company for failure to provide this type of evidence. The only reasonable evidence that can be provided is therefore add-on data and the effectiveness of monotherapy has to be imputed from the	Technology Appraisal 2013 for further information. The Committee did not consider the any anticipated price fall associated with patent expiry because a specified price has to be available and guaranteed across the NHS (see section 5.5 of the Guide to the methods of technology appraisal 2013).

Role*	Section	Comment [sic]	Response
		LDL reduction vs CHD rate data. We believe that NICE also need to be aware of tolerability of the recommended add on therapy that they are suggesting. If we are not to use ezetimibe as an add on therapy, in patients with high risk and those with heterozygous FH, we are left to use other, non-evidence based treatments. Ezetimibe is, on the whole, well tolerated by patients, whereas the bile acid sequestrants are less well tolerated and more expensive thatn ezetimibe, and therefore it is difficult to achieve a dose that patients can tolerate and achieve the lipid lowering effects required. We believe it is wholly unethical to withhold ezetimibe from patients who remain at high risk, be that due to inability to tolerate high dose statins or where they have significant co morbidities. The committee has also not taken into account the short period of time that ezetimibe has left on patent, meaning that the costs are likely to significantly decrease in 2018. We believe that in line with the evidence and NICE CG 181, that ezetimibe should be used as add on therapy for those patients who are not to target with the LDL cholesterol, and as monotherapy for those with high cardiovascular risk, who are unable to tolerate statins.	

MSD Response to NICE ACD for ezetimibe

MSD welcomes the opportunity to comment on the appraisal consultation document (ACD) for ezetimibe.

There are particular groups of patients that will be disadvantaged if this preliminary guidance[1] is made final, which include:

- People with heterozygous familial hypercholesterolaemia (HeFH);
- High-risk primary prevention patients, especially those with type 2 diabetes mellitus;
- High-risk secondary prevention patients.

MSD made a clear clinical and cost-effectiveness case for treating these patient groups with ezetimibe co-administered with a statin, where dose titration of the statin is inappropriate and/or limited by intolerance. If this recommendation becomes final, there would be no other treatment option for these patients given the recommendations in NICE Lipid Modification Clinical Guideline, CG181[2]. The beliefs and actions by the ERG and Committee regarding the evidence base and economic arguments have led to what we believe is a flawed preliminary recommendation.

The following summarises the key issues for each of these patient groups, and these are outlined in more detail in the following pages:

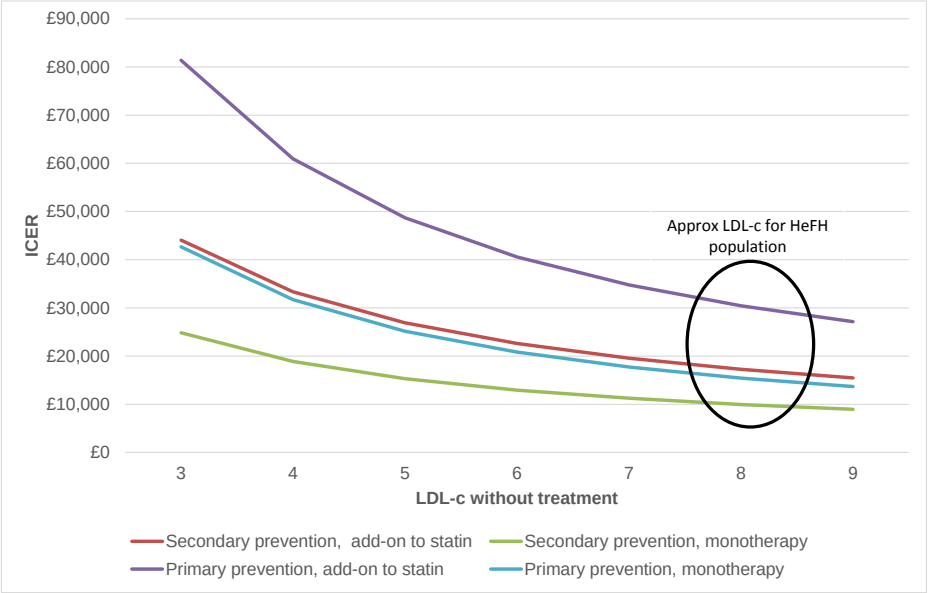
- People with HeFH:
    - failure to consider all the evidence for these patients, including the impact of higher baseline LDL-c levels, which has resulted in a lack of a recommendation for the use of ezetimibe as an add-on to statin in this extremely high-risk patient group.
- High-risk primary prevention patients, especially those with type 2 diabetes mellitus:
    - failure to consider the impact of increasing 10-year cardiovascular (CV) risk levels above 20% when considering cost-effectiveness.
- High-risk secondary prevention patients:
    - While the Committee has accepted the relationship between LDL-c and CV event reduction based on the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis[3] and using this in the cost-effectiveness model for the primary prevention and ezetimibe monotherapy populations, we are concerned by the failure of the Committee to recognise that IMPROVE-IT[4] is consistent with the CTTC meta-analysis;
    - the inappropriate use of the IMPROVE-IT data in the cost-effectiveness model to analyse the impact of using ezetimibe as add-on to statin in this patient group.

Finally, we are disappointed that the Committee has not taken into account the future budget impact of ezetimibe, reflecting ezetimibe's impending patent expiry in April 2018.

1. People with Heterozygous Familial Hypercholesterolaemia

We are concerned that all the relevant evidence submitted by MSD with respect to patients with HeFH has not been considered in developing the ACD, which has led to a lack of a recommendation in the add-on to statin population. The scope outlines that people with HeFH are a relevant sub-group and clinical and cost-effectiveness evidence for this sub-group has been provided by MSD (Section 4.8 and Section 5.9.2, Manufacturer's submission[5]). The key summary of the cost-effectiveness estimates from the submission are summarised below, based on extrapolating the base case results to higher baseline LDL-c levels seen in people with HeFH (at least 8 mmol/L)[6,7]. As highlighted by the analysis, the cost-effectiveness of ezetimibe increases at higher baseline LDL-c levels.

Figure 1 Incremental cost-effectiveness ratios (ICERs) for base populations, by varying baseline LDL-c levels



While the following is stated on page 45 of the ACD, there is no mention of the cost-effectiveness evidence considered and the conclusion reached by the Committee for the HeFH population with respect to ezetimibe monotherapy or adding-on ezetimibe to statin under section 4 of the ACD ('Considerations of the evidence')[1]:

"*The committee was aware of evidence from 4 clinical trials in adults with type 2 diabetes, a trial in patients with chronic kidney disease and a trial in patients with heterozygous familial hypercholesterolaemia. The Committee considered the cost-effectiveness estimates for the subgroups presented by the company*" and cross-references to section 3.7 and 4.18.

The preliminary recommendation in the ACD recommends the restricted use of ezetimibe as monotherapy for patients with non-familial hypercholesterolaemia, as well as in those patients with HeFH using the same criteria. This conclusion is inconsistent with the cost-effectiveness evidence submitted by MSD, which showed by extrapolating the cost-effectiveness estimates to high baseline LDL-c levels, ezetimibe is clearly a cost-effective option for patients with HeFH in both monotherapy when a statin is considered inappropriate or is not tolerated, as well as add-on statin.

MSD believes that the cost-effectiveness evidence related to HeFH has not been adequately considered by the Committee in drafting the ACD. The NICE Committee is requested to review all the clinical and cost-effectiveness data and consider the appropriate recommendation for this group at very high-risk of experiencing cardiovascular events.

2. High-risk primary prevention patients, especially those with type 2 diabetes mellitus

Among the primary prevention patients, there are particular cohorts at high-risk of cardiovascular disease, for example, those with high baseline LDL-c levels or patients with co-morbidities such as diabetes. Patients with diabetes, for example, are at two to three times higher risk of cardiovascular events compared to those without diabetes[8].

MSD believes that one of the key factors impacting cost-effectiveness of primary prevention patients has not been fully considered. The ERG has recognised that "*Decreasing the 10-year cardiovascular risk to 10%...*" increased the ICER (section 3.32, ACD[1]), however, they have not identified and recognised that increasing the 10-year CV risk from 20% to 30% also has a significant impact on the ICERs for the primary prevention populations. Scenario analyses evaluating the impact of increasing the 10-year CV risk levels were submitted by the manufacturer in the following sections in the submission[5] with the corresponding ICERs:

- Primary prevention, add-on to statin, 30% 10-year CV risk, ICER: £41,783 per QALY (Table 71, page 174)
- Primary prevention with diabetes, add-on to statin, 30% 10-year CV Risk, ICER: £22,335 per QALY (Table 83, page 187)

There is no evidence in the ACD that the Committee has considered the ICERs for the primary prevention population and the primary prevention sub-group population with type 2 diabetes, when the 10-year CV risk is increased to 30%. As a consequence, MSD believes that key evidence submitted by the manufacturer and the consideration of high-risk patient cohorts, such as the diabetes population, which are cost-effective, has been overlooked in developing the ACD.

As such, MSD requests the following:

- Firstly, section 3.32 in the ACD is updated to accurately reflect that a decrease **or** an increase in the 10-year CV risk impacts the ICERs. The text should be updated to the following:
  "*Changing the 10-year cardiovascular risk to 10% or 30%, which increased the ICER to £47, 067 per QALY or decreased the ICER to £21,187 per QALY gained.*"
- Secondly, the Committee considers the impact of increasing as well as decreasing the 10-year CV risk on the ICERs for the primary prevention population, including the sub-group with diabetes add-on to statin, as this evidence originally submitted by MSD does not appear to have been adequately considered – omitting the potential consideration of relevant cohorts (e.g. primary prevention with diabetes, add-on to statin with a 30% 10-year cardiovascular risk) that are cost-effective.

3. High-risk secondary prevention patients

MSD is concerned by the belief of the ERG and the Committee that it was more appropriate to use the IMPROVE-IT clinical data to model the 'secondary prevention, add-on to statin' population rather than using the CTTC meta-analysis (section 4.15, ACD[1]). This approach would only be applicable if we were evaluating the benefit of adding on ezetimibe in patients with the same characteristics of those in the IMPROVE-IT trial[4], in particular those who had low baseline LDL-c and had low residual risk of further CV events. This is explained in further detail below.

The IMPROVE-IT study population is a sub-set of the secondary prevention population

IMPROVE-IT[4] put two hypotheses to the test. The first is that lowering LDL-c from an already low to an even lower level is better, with the results demonstrating that the LDL-c hypothesis from CTTC meta-analysis holds for very low levels of cholesterol. The second is that adding another LDL-lowering agent to a statin decreases cardiovascular outcomes (which no other non-statin has demonstrated). To do this, the trial was designed so that the statin plus placebo (control) group would achieve 'at goal' LDL-c level (<1.8 mmol/L on average)[9] while the statin plus ezetimibe group, by nature of the additional LDL-c reduction afforded by ezetimibe, would achieve an LDL-c level of about 1.4 mmol/L or less.

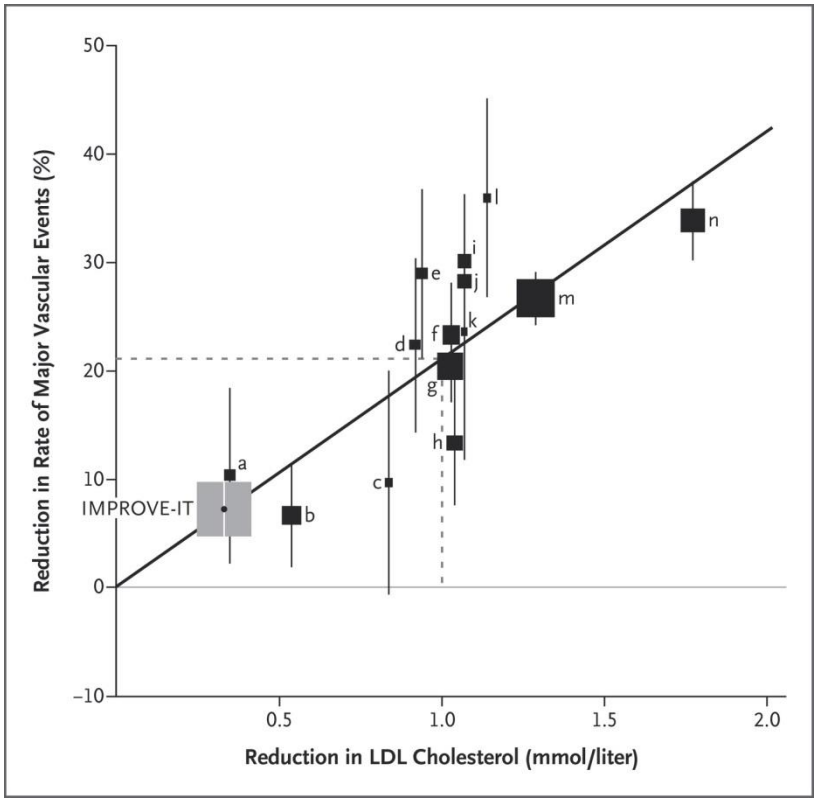
The study was conducted in a very specific population presenting with stabilised ACS and low pre-treatment baseline LDL-c levels (mean 2.4 mmol/L). Ezetimibe was evaluated to assess the incremental clinical benefit in a well-treated population on statin with a very low LDL-c. Hence the IMPROVE-IT population is a sub-set of the wider secondary prevention add-on to statin population that would typically be treated with ezetimibe in the real world. The IMPROVE-IT population is therefore not reflective of the patients routinely treated with ezetimibe in UK clinical practice, where their baseline LDL-c levels are much higher[10].

The clinically relevant (and modelled) population

Ezetimibe is currently used in patients that do not achieve sufficient LDL-c lowering on statins, for example, where statin uptitration is limited by intolerance or because of high baseline LDL-c levels; this was the population modelled in the submission. IMPROVE-IT did not examine this population. Therefore in order to model a more clinically relevant population, MSD took the approach of using the LDL-c hypothesis from the CTTC meta-analysis to estimate ezetimibe's treatment benefit in the modelling approach.

The IMPROVE-IT and SHARP studies are consistent with the LDL-c hypothesis from the CTTC meta-analysis

Figure 2. Plot of the IMPROVE-IT trial data and statin trials for change in LDL-c versus clinical benefit[4].



The CTTC meta-analysis of all major statin studies (n=169,138) has established a linear relationship between the absolute reduction in LDL-c and the proportional reduction in major vascular events, where a reduction in LDL-c of 1 mmol/L reduces the incidence of major vascular events by 22%[3]. Hence, a 0.5 mmol/L absolute reduction in LDL-c, reduces the incidence of major vascular events by 11%. This well-accepted analysis was used as the basis for the economic model in the original NICE TA132 review in 2007 and has also been accepted by the Committee for modelling the primary prevention and monotherapy populations in this current review, which MSD supports[1, 12].

In the IMPROVE-IT study, the corresponding mean LDL-c levels at year one were 1.42 mmol/L in the ezetimibe/simvastatin group vs. 1.86 mmol/L in the simvastatin group, a difference of 0.43 mmol/L. Extrapolating the clinical benefit to a per mmol/L basis of LDL-c reduction with ezetimibe in IMPROVE-IT, resulted in a Hazard Ratio (HR) of 0.80 (95% CI [0.68; 0.94]), which is consistent with the HR 0.78 (95% CI [0.76; 0.80], p<0.0001) observed with statins in the meta-analysis performed by the CTTC in 2010 (Figure 1)[3]. Furthermore, in the SHARP trial, an average reduction of 0.85 mmol/L yielded a significant 17% reduction in major atherosclerotic events, again similar to the effects seen in the CTTC meta-analysis[12].

As can be seen in Figure 2, the LDL-c/cardiovascular event reduction relationship obtained by ezetimibe in IMPROVE-IT sits on the CTTC line, and therefore is consistent with (and was predicted by) the CTTC meta-analysis[4,13,14]. Thus, demonstrating that a 1 mmol/L reduction in LDL-c with ezetimibe would lead to a 22% reduction in the incidence of major vascular events.

MSD is concerned to hear that despite this unequivocal scientific evidence and the support of clinical experts[15], member(s) of the Committee question whether the IMPROVE-IT study was consistent with the CTTC meta-analysis.

It is inappropriate to use the IMPROVE-IT data to analyse the impact of using ezetimibe as add-on to statin in the overall secondary prevention patient population

For patients that have higher baseline LDL-c levels, a higher expected absolute reduction in LDL-c with lipid-lowering therapy is expected, and therefore, based on the CTTC meta-analysis, a larger reduction in the incidence of major cardiovascular events.

The relative risk reduction in cardiovascular events observed in the IMPROVE-IT study is representative of an additional mean LDL-c reduction of 0.43 mmol/L with simvastatin and ezetimibe compared to simvastatin alone. The relatively small absolute LDL-c reduction in this study was expected due to the low baseline LDL-c levels, and as highlighted above, is consistent with the LDL-c hypothesis from CTTC meta-analysis.

In the target population under consideration for this appraisal, much larger absolute LDL-c reductions are expected as patients are expected to have a higher pre-statin baseline LDL-c level of at least 4.32 mmol/L (Section 5.2, Manufacturer's submission[5]). By applying the expected percentage LDL-c reduction derived from the revised manufacturer's meta-analysis of an additional reduction of 15.6% (95% CI 17.05 to 14.13) to a baseline of 4.32 mmol/L, this results in an expected LDL-c reduction of 0.67 mmol/L. This is much larger than that observed in IMPROVE-IT due to the higher baseline LDL-c levels of the patients that are currently treated with ezetimibe.

As such, the relationship between LDL-c and cardiovascular events from the CTTC meta-analysis was used to extrapolate to this larger absolute LDL-c reduction and derive relevant treatment effect estimates for ezetimibe that were applied in our model. For a 0.67 mmol/L absolute LDL-c reduction, this corresponds to a RR of 0.83 for non-fatal MI and 0.90 for non-fatal stroke. These are much higher than observed in the IMPROVE-IT study because of the larger expected reductions in LDL-c, but are the appropriate estimates for the treatment effect of ezetimibe in a secondary prevention, add-on to statin population with a pre-statin baseline LDL-c of 4.32 mmol/L.

Therefore, it is inappropriate to apply the fixed RR from the IMPROVE-IT study to the secondary prevention add-on to statin population in the submission. Furthermore, as highlighted by Figure 1, in our modelling approach based on CTTC meta-analysis relationship, the cost-effectiveness of ezetimibe increases as the baseline LDL-c levels increase, and this is because the expected absolute LDL-c reduction is greater (see Figure 1 and Figure 40, Manufacturer's submission[6]).

By using the IMPROVE-IT treatment effect estimates in the economic model for the clinically relevant 'secondary prevention, add-on to statin' population, the benefit associated with ezetimibe is significantly underestimated, thereby overestimating the ICERs. The relationship between LDL-c and cardiovascular outcomes from the CTTC meta-analysis is the only appropriate way to model the cost-effectiveness of the secondary prevention, add-on to statin population, as well as the additional cohorts such as monotherapy and primary prevention.

MSD is extremely disappointed by the Committee and the ERG for the inappropriate application of the IMPROVE-IT data in developing the preliminary recommendation, and the negative consequences this will have on patients if these are made final in their current form. The current

recommendation would deny patients at the highest risk access to a treatment option that would avoid further cardiovascular events.

4. Use of cholesterol targets in current clinical practice (Section 4.2, ACD)

The Committee has recognised that one of the key changes in the updated NICE Clinical Guideline for Lipid Modification (CG181)[2] published in July 2014 was a greater emphasis on managing cardiovascular risk rather than meeting a specific cholesterol target. However, the Committee has failed to adequately recognise that cholesterol targets are routinely used in clinical practice, and will remain so for the foreseeable future.

A large number of patients are still not reaching recommended cholesterol levels. In 2011, the Health Survey for England reported that 60% of men and 38% of women with CVD (the expectation is that the majority had received advice on lifestyle modification and drug treatment where deemed advisable) had TC levels below 5 mmol/L (the NICE CG675 'audit level' for those with CVD, diabetes or hypertension who are on drug treatment), while only 27% and 10% respectively had levels below 4 mmol/L (the then-NICE 'target level' for this high-risk group) in 2011[16]. As evident, there is an opportunity to further reduce the risk of future major cardiovascular events in such patients by further reducing TC and LDL-c with the use of ezetimibe.

A recent report from Soran *et al.* has shown that whilst CVD risk is useful in determining treatment, the LDL-c reduction achievable is critical.[17] They showed that pre-treatment LDL-c concentration has a large determining factor on the individual that benefits treatment – those with high pretreatment LDL-c (largest absolute change on treatment) and greatest CVD risk, benefit more from lipid lowering therapy and have lower NNTs (number needed to treat). Lack of LDL-c targets and a focus on CVD risk benefits people with lower pre-treatment LDL-c, whereas people with more marked hypercholesterolaemia benefit more from specific targets.

The positioning of ezetimibe and cost-effectiveness estimates should be considered by the Committee in light of the common use of cholesterol targets in clinical practice – and recognising the benefit that can be offered to patients that are not appropriately controlled on the maximum tolerated dose of statin by adding in ezetimibe and further reducing their risk of major CV events. The patients that could benefit most from ezetimibe are those at the highest risk of experiencing cardiovascular events, such as those with existing CVD (secondary prevention), or co-morbidities such as CKD or diabetes.

5. Baseline LDL-c levels is a key factor impacting cost-effectiveness

In section 3.32 of the ACD[1], there is a summary of the key parameters that the ERG has determined had the greatest impact on the ICER. Varying baseline LDL-c levels also has a significant impact on the ICERs and this is not a factor currently listed in this section.

For the base case analyses for the primary and secondary prevention populations, and the chronic kidney disease and diabetes sub-groups, the base case assumed a baseline LDL-c pre-statin treatment of 4.32 mmol/L (see section 5.2, Manufacturer's submission[5]). Scenario analyses evaluating the impact of alternative pre-statin LDL-c levels on the cost-effectiveness estimates were submitted by the manufacturer and shown in the following figures in the submission: figures 1, 40,

42 and 49. Figure 1 above, taken from the manufacturer's submission, summarises the impact on the base case populations and the primary prevention with diabetes sub-group.

There is no evidence in the ACD that the NICE Committee have considered the impact of altering baseline LDL-c, pre-statin treatment levels on ICERs, where at higher baseline LDL-c levels, the cost-effectiveness of ezetimibe increases. As such, MSD requests the following:

- Firstly, section 3.32 in the ACD is updated to add an additional bullet reflecting the significant impact of altering baseline LDL-c levels, for example:
  "*Changing the baseline LDL-c levels, where at higher baseline LDL-c levels, the cost-effectiveness of ezetimibe increases…*"
- Secondly, the NICE Committee considers the impact of altering the baseline LDL-c levels on the ICERs for all the modelled populations.

6. Direct meta-analysis of clinical outcomes (Section 3.11, ACD)

MSD disagrees with the ERG's view that the manufacturer should have conducted a direct meta-analysis of clinical outcomes as it would provide no relevant information for this appraisal. Ezetimibe has been studied in three CV outcomes trials in three very distinct populations, SEAS[18], SHARP[12] and IMPROVE-IT[4]. Two of these have studied ezetimibe + statin versus placebo, a comparison that is not relevant to this review of TA132 and this has been acknowledged and agreed by the Committee (see section 4.5, ACD[1]). The IMPROVE-IT trial compared ezetimibe + statin versus statin which is relevant to this review, therefore one CV outcomes trial becomes relevant evidence for the populations under review.

In 2015, two meta-analyses evaluating ezetimibe's effect on CV outcomes have been published, and both of these reaffirm the view that only three trials have been designed to appropriately evaluate the effect of ezetimibe on CV outcomes[19,20]. MSD believes that this statement from the ERG in section 3.11 of the ACD should be removed as a direct meta-analysis of clinical outcomes, as suggested by the ERG, would provide no relevant information for this appraisal.

7. Non-CV Death benefit

The Committee has assumed the following with respect to modelling the treatment effect of ezetimibe for the cost-effectiveness model (section 4.15, ACD):

"*It noted the ERG's comment that there was no statistical association between LDL-c and non-cardiovascular related deaths in the CTTC meta-analysis, and concluded it was unreasonable to assume that the treatment effect of ezetimibe should apply to non-cardiovascular related deaths*"

While this is consistent with the approach taken in the original TA132 review[21], this differs from the approach taken in the latest Clinical Guideline, CG181[2], published in July 2014 where the most plausible estimates for non-CV death were applied. As part of this guideline, the treatment effect related to statin versus placebo for the add-on to statin analyses was derived from a meta-analysis of RCT data with CV endpoints and used to model the treatment benefit associated with statins in the economic analyses; the same data was applied in our model. The treatment effect estimates of ezetimibe used in our model are derived from the CTTC meta-analysis of 26 RCTs. As such, MSD modelled the non-CV benefit using the most plausible estimates to be consistent with the most

recent approach taken by NICE (NICE CG181), and explored the uncertainty associated with this through one-way sensitivity analysis and PSA. By the ERG taking the approach stated in the ACD there is an inconsistency in the approach taken to producing NICE guidance.

8. Ezetimibe's patent expiry in 2018

The patent for ezetimibe expires in two years' time and MSD is disappointed that the Committee has not taken this into account as part of their decision making. As highlighted with the manufacturer's submission, significant price falls are expected upon patent expiry in-line with other lipid-lowering therapies, and the ICERs for ezetimibe fall substantially under the £20,000 per QALY threshold when this is applied in year 3 onwards of the analysis using a conservative 75% price reduction.

References

1. National Institute for Health and Care Excellence, Appraisal Consultation Document, Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (review of NICE technology guidance 132), October 2015
2. National Institute for Health and Care Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (CG181). National Institute for Health and Care Excellence; 2014; Available from: http://www.nice.org.uk/guidance/cg181 Last accessed 05 November 2015
3. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010; 376(9753):1670-1681.
4. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015
5. Merck Sharp & Dohme, Manufacturer's submission, Single technology appraisal, Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia [ID627], June 2015
6. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008; 358(14):1431-1443
7. Neil A, Cooper J, Betteridge J, Capps N, McDowell I, Durrington P et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J 2008; 29(21):2625-2633
8. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. Circulation 1979; 59(1):8-13
9. Grundy SM, Cleeman JI, Merz CNB, Brewer HB, Clark LT Jr, Hunninghake DB; Pasternak RC, Smith SC Jr, Stone NJ, for the Coordinating Committee of the National Cholesterol Education Program. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004;110: 227-239
10. Laufs U, Descamps OS, Catapano AL, Packard CJ. Understanding IMPROVE-IT and the cardinal role of LDL-C lowering in CVD prevention. Eur Heart J. 2014 Aug 7;35(30):1996-2000
11. National Institute for Health and Care Excellence. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. National Institute for Health and Care Excellence; 2007; Available from: http://www.nice.org.uk/guidance/ta132; Last accessed 05 November 2015
12. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011; 377(9784):2181-2192
13. Jarcho JA, Keaney JF Jr. Proof That Lower Is Better: LDL Cholesterol and IMPROVE-IT. N Engl J Med 2015; 372:2448-2450
14. Masana L, Pedro-Botet J, Civeira F. IMPROVE-IT clinical implications. Should the "high-intensity cholesterol-lowering therapy" strategy replace the "high-intensity statin therapy"? Atherosclerosis 2015; 240: 161-162
15. NICE. Clinical Expert Statements. Single Technology Appraisal. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132) – Committee Papers. October 2015. Available from: http://www.nice.org.uk/guidance/GID-TAG326/documents/committee-papers; Last accessed 09 November 2015
16. Health & Social Care Information Centre (HSCIC). Cardiovascular Disease. Health & Social Care Information Centre (HSCIC); 2012
17. Soran H, Schofield JD, Durrington PN. Cholesterol, not just cardiovascular risk, is important in deciding who should receive statin treatment. *Eur Heart J.* 2015; doi:10.1093/eurheartj/ehv340
18. Rossebo AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008; 359(13):1343-1356

19. Savaresea G, De Ferrarib GM, Rosanoc GMC and Perrone-Filardi P. Safety and efficacy of ezetimibe: A meta-analysis. Int J Cardiol 2015; 201: 247-252
20. Battaggia A, Donzelli A, Font M, Molteni D, Galvano A. Clinical efficacy and safety of Ezetimibe on major cardiovascular endpoints: systematic review and meta-analysis of randomized controlled trials. PLoS One; 10(4): DOI: 10.1371/journal.pone.0124587
21. Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A et al. Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. Ara, R Tumur, I Pandor, A Duenas, A Williams, R Wilkinson A Paisley, S Chilcott, J ; 2008 Available from: http://www.journalslibrary.nihr.ac.uk/ data/assets/pdf file/0019/65206/FullReport-hta12210.pdf; Last accessed 05 November 2015

British Hypertension Society
Committed to preventing cardiovascular disease

Executive Committee:
President: Associate Professor A Brady
Vice-President: Professor F Cappuccio
Secretary: Dr T McCormack
Treasurer: Mrs N Stetson
Ordinary Members: Dr C McEniery, Dr U Martin, Dr P Robinson, Dr W Sunman

Registered Charity No: 287635 **www.bhsoc.org**

Address for Correspondence:

British Hypertension Society Administrative Officer, c/o Hypertension Research Team, Clinical Sciences Wing, Glenfield Hospital, Leicester LE3 9QP
Tel: 0116 2502605 Email: bhs@le.ac.uk Website: www.bhsoc.org

11 November 2015

British Hypertension Society Comments on the appraisal of Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132) [ID627]

The BHS welcomes NICE guidance on the use of ezetimibe following publication of the IMPROVE-IT trial, in the New England Journal of Medicine in 2015. The IMPROVE-IT trial showed the expected benefit of a 23% reduction in LDL cholesterol, from 1.8mmol/L vs. 1.39mmol/L, by adding ezetimibe 10 mg to a statin. The IMPROVE-IT trial studied patients already at low cholesterol levels, following the trial design. At such low levels of cholesterol the many meta-analyses of LDL lowering v outcome from the major statin trials predict about an 8% benefit in relative risk reduction of major cardiovascular events (e.g., CTTC Lancet 2010; 376:1670-81, LaRosa JC et al. N Engl J Med 2005;352). This was achieved in the IMPROVE-IT trial (e.g., 10% reduction in cardiovascular death, non-fatal MI and non-fatal stroke). Thus the premise of the NICE 2007 TA132 Ezetimibe guidance, that the benefit of ezetimibe was related, like statins, to the degree of LDL lowering, has been proven to be correct.

However, a survey among BHS members has shown that prescribing of Ezetimibe in usual practice is to achieve, in secondary prevention, a target cholesterol for an individual already on a statin but not at target. For example, select an individual on maximal tolerated statin with an achieved cholesterol of 5.2 mmol/l. Adding ezetimibe typically reduces cholesterol from 5.2 to about 4.2 mmol/l. This reduces CV risk by 22%.

Calculations of QALYs and ICERs depend on the cost to achieve meaningful risk reduction. In the UK, ezetimibe is not used as it was in the IMPROVE-IT trial to reduce an already low LDL cholesterol to an even lower degree. This is not cost-effective. But to reduce risk by 22%, for the QALY costs shown in NICE TA132 (typically the practice in the UK) is in our view reasonable use of healthcare resources, for those individuals remaining at high CV risk despite optimal use of statins.

Calculating QALYs on an 8% relative risk reduction makes ezetimibe uneconomic. But this is not how ezetimibe is used in clinical practice in the UK.

Moreover, the patent on Ezetimibe expires in 2018. Calculations for cost per QALY and for ICERs often use a 5 or 10 year prediction. In 2018 generic Ezetimibe will likely be relatively inexpensive, so 10 year calculations of cost should take this into account.
In summary, the BHS believes that the current use of Ezetimibe in the UK is correct, used mostly to achieve target cholesterols for individuals in secondary prevention already optimally treated with statin. We believe that the cost calculations in NICE TA132 are correct, and the benefits from Ezetimibe in the IMPROVE-IT trial were as predicted by the CTTC and other meta-analyses.
With regard to ezetimibe monotherapy for statin-intolerant patients, the BHS is less secure. But in the absence of data for any other drug ezetimibe at least has good safety data, with cholesterol-lowering ability, so the BHS offers no specific other recommendation.

HEART UK
THE CHOLESTEROL CHARITY

T: 01628 777046
W: www.heartuk.org.uk

10th November 2015

ACD - Consultees & Commentators: (Hypercholesterolaemia - ezetimibe (review TA132)) [627]

HEART UK is the Nation's Cholesterol Charity providing expert support, guidance and education to individuals with raised cholesterol, atherosclerosis and other lipid conditions. To this aim the charity provides high quality literature, a Cholesterol Helpline, a Patient Charter, an extensive website, a range of educational videos, the Ultimate Cholesterol Lowering Plan© and a range of electronic communication tools aimed at increasing the awareness of cholesterol.

HEART UK also supports the health care professionals who work and care for patients (and their families) with raised and unhealthy patterns of high cholesterol and other dyslipidaemias. HEART UK hosts a world class annual scientific conference and other networking events for clinicians, researchers, GP's, nurses and dietitians. The charity maintains a health professional membership scheme, provides resources and training to health care professionals.

In addition the charity campaigns hard to keep cholesterol and cardiovascular disease at the top of the political agenda and to help ensure better identification, diagnosis and treatment of patients with the aim of preventing deaths from early and avoidable cardiovascular disease.

HEART UK works directly with lipid experts in lipid clinics and specialist GP services where the diagnosis, treatment and the on-going management of complex lipid conditions such as Familial Hypercholesterolaemia (FH) Familial Combined Hyperlipidaemia (FCH), Type 3 Hyperlipidaemia and Lipoprotein Lipase Deficiency (LPLD) take place. In addition these centres support people with complex secondary dyslipidaeamias, secondary to and alongside other co-morbidities. Lipid clinics also support patients that have suspected statin intolerance; the aim being to identify a level of treatment and lifestyle advice that provides some protection but with minimal side effects.

The majority of individuals diagnosed with a primary dyslipidaemia will require lifelong treatment with cholesterol lowering medication in order to reduce their chances of early and avoidable death from coronary heart disease. These patients are often highly motivated to make changes to their diet and lifestyle and to maintain regular medication.

Recent successes in generating awareness of the dangers of high cholesterol and in identifying individuals with raised cholesterol have resulted in an increase popularity of the Cholesterol Helpline, and the charities website and social media networks resulting in the need for extra resource to

HEART UK
THE CHOLESTEROL CHARITY

T: 01628 777046
W: www.heartuk.org.uk

support these communications especially the helpline.

HEART UK wishes to let it be known of our overall disappointment with this initial recommendation, which leaves a significant number of patients at a disadvantage.

In this letter of response I wish to detail the concerns of HEART UK:

1. (4.21) The main problem in this ACD is the lack of mention of familial hypercholesterolaemia - the most significant use of Ezetimibe and recommended in CG71 and a formal comment on continued use in FH needs to be included.

In FH the population attributable to risk due to LDL-C is greater than in the general population being 50-70% rather than 30-50%- see clinical expert comments for CG71 and the appraisal of Evolocumab. The recent TA on Evolocumab was able to determine the health economics in FH using a multiplier applied to the basic CVD event model of x7 (Benn et al) with sensitivity down to x 3.5. This should be viewed in parallel with this ACD to allow consistency across lipid interventions.

In addition, an intervention with formal outcomes evidence for add-on prescription to a statin (Ezetimbe in IMPROVE-IT) and considerable clinical safety data following from many years of prescribing should be preferred to a novel agent with greater efficacy on a surrogate outcome (LDL-C) but no long term safety or efficacy data.

2. (4.17) The recommendation of not using Ezetimibe in secondary prevention (established CVD) as an add-on to statins are at odds with clinical evidence and current clinical practice for management of patients with raised LDL-C post statin therapy.

The model assumes a uniform risk for a secondary prevention whereas the reality is that this population includes multiple sub-groups with higher event rates - patients with acute coronary syndromes (for event rates see REACH registry -50% excess compared to stable coronary artery disease- as used in Evolocumab TA; and also the exact trial population investigated in IMPROVE-IT); type 2 diabetes with established stable CVD - a common clinical group (see Robinson JG & Stone N; Am J Cardiol 2006; 98: 1405 for NNT vs LDL-C risk curve for different sub-groups) ; as well as a population with lower event rate (chronic stable angina) but high propensity to undergo percutaneous coronary intervention for symptomatic coronary artery disease. Thus angina needs to be included in the model allied with modelling the reduction in need for PCI which in CTT exceeds that for non-fatal MI and is approximately 50% over a 5 year horizon. A scenario analysis for different post-statin treatment LDL-C concentrations in these groups would be interesting and clinically

HEART UK
THE CHOLESTEROL CHARITY

T: 01628 777046
W: www.heartuk.org.uk

relevant.

The Lipid Modification guideline CG67 made a distinction between acute coronary syndromes and stable CVD based on event rates (e.g REACH regsitry) and found higher dose high efficacy on-patent statins cost-effective. In CG181 high efficacy statin costs had reduced so treatment of both ACS and general chronic CVD was cost-effective using highest dose statin therapy. The health economic analyses by Ara (Ara R et al; Eur J Prev Cardiol 2012; 19; 474 & Exp Rev Pharmaecon Outcome Res 2009; 9 : 423) are interesting analogies (with added scenario models) to the current decision problem as the efficacy of Ezetimibe is similar to titration from low dose generic to high dose high efficacy on-patent statin (16-20% added LDL-C reduction; £26 per month excess costs). It found high-cost statins to be cost-effective in ACS- as did CG67. The data for the Ezetimibe model for secondary prevention (in the higher high ACS sub-group) should be similar and thus scenario B is probably overly conservative and scenario A (with modifications) likely closer to the real world.

3. As stated in CG181 patients with CKD3+ are at very risk for CVD events. The use of high dose high efficacy statin in CKD3+ is limited by the excess drug toxicity of statins in this patient group. In addition the large and well conducted SHARP trial provides an evidence base for a 17% CVD event reduction in this patient group where statin monotherapy had been ineffective (Wanner C et al; Atorvastatin 20mg in 4D trial in CKD5; NEJM 2005; 353: 238; Fellstrom R et al AURORA Rosuvastatin 20mg in CKD3-4; NEJM 2009; 360: 1395) despite significant LDL-C reductions. Ezetimibe should be recommended for management of CVD risk in patients with CKD3+ given the trial evidence and as a non-lipid associated benefit of combination statin-Ezetimibe therapy cannot be completely excluded.

On a final note;
4. (4.9) The SEAS trial (of combined Simvastatin 20mg & Ezetimibe 10 mg) had a complex primary combined endpoint comprising both valve and CVD outcomes. The prespecified secondary analysis of CVD outcomes alone (underpowered) showed a 22% reduction in events.

NICE have disadvantaged patients with heterozygous familial hypercholesterolaemia because the baseline risk has been taken as the same as the general primary prevention population with equivalent LDL cholesterol, whereas it is much higher due to lifelong exposure to high cholesterol. Consequently, the advice not to use risk calculation algorithms has been abandoned: possibly inadvertently.

The benefit of statins are related to the absolute LDL lowering and the pretreatment risk, thus a 50% reduction in LDL cholesterol will leave patients with higher LDL cholesterol compared with non-

HEART UK
THE CHOLESTEROL CHARITY

T: 01628 777046
W: www.heartuk.org.uk

familial hypercholesterolaemia. The modelling would better include notional targets of LDL cholesterol achieved by a 50% reduction.

The current modelling based on the existing economic model has led to advice which may not be correct in that Ezetimibe can only be added to statin for secondary prevention in the familial hypercholesterolaemia population. Statin intolerance is one situation where Ezetimibe monotherapy has been found to be cost effective, likely based on the higher pre-treatment LDL cholesterol compared with patients on statins where the absolute extra LDL cholesterol lowering would be smaller. Patients with familial hypercholesterolaemia may well be left with an LDL cholesterol of 4, 5, or 6 mmol/L higher on maximum statin treatment.

The recommendation indicates that Ezetimibe might be considered in patients who are intolerant of statins but statin intolerance is not defined and there is a risk that patients will be started on Ezetimibe rather than exploring all statin based options. This would be neither clinically nor cost effective.

The way that the modelling has used post-statin LDL cholesterol in addition to underestimation of the baseline risk in familial hypercholesterolaemia both disadvantage this high risk patient group.

I hope you find these comments useful and that NICE re-considers its recommendations in light of these, offering access to a greater number of patients that will benefit from Ezetimibe and not disadvantaging a significant high risk patient group.

British Heart Foundation, Response to Consultation on appraisal of Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132) [ID627].

November 2015

So far as we are aware, all the relevant evidence has been taken into account, and the provisional recommendations are a sound and suitable basis for guidance. We note the use of the 20%, 10 year CVD risk as the threshold for treatment, and think this will require careful communication to clinicians in the field. We are not aware of any aspects of the recommendations that need particular consideration to ensure unlawful discrimination is avoided, although we note the absence of any advice regarding the use of ezetimibe in pregnant women.

For further information, contact [redacted], [redacted]

The Royal College of Pathologists
Pathology: the science behind the cure

Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132) [ID627]

The Royal College of Pathologists would like to thank you for the opportunity to comment on the Appraisal Consultation Document of this technology appraisal.

General Comments

This document lacks the clinical perspective of the original document having dispensed with the introductory section describing the context in which the technology is used and omitting the entire Section 2 from the previous version which covered “Clinical Need & Practice”.

These sections in the previous document included definitions of intolerance to initial statin therapy (2007 1.6) and Hypercholesterolaemia (2007 2.1). Inclusion of these definitions is essential as they are a basis for clinical recommendations and the guidance cannot be properly interpreted or implemented without them. Overall the document is poorly structured in comparison to the 2007 document and it would be preferable if the revised document followed the original structure and major section headings.

Specific Comments

1. Preliminary Recommendations

1.1 The recommendation conflicts with both CG71 and CG81 and recommending that primary heterozygous familiar hypercholesterolemia patients are assessed using the QRISK2 risk assessment tool. In CG81, patients with familial hypercholesterolemia, chronic kidney disease (CKD3+) and type 1 diabetes are specifically excluded from QRISK2 risk assessment. The stated definition of patients eligible for Ezetimibe requiring lipid modification for primary prevention is those having both type 2 diabetes and a risk greater than 20%.

CG181 recommends risk assessment in type 2 diabetes patients using the QRISK2 risk tool, it makes no sense to restrict consideration of this technology only to those patients above 20% who have type 2 diabetes as these are at no greater risk than other patients at greater than 20% cardiovascular risk. There is no evidence that the technology has superior efficacy in primary prevention in type 2 diabetes patients. Choice of risk threshold of 20% or greater 10 year risk appears to be an arbitrary decision. In CG181 a 10 year cardiovascular risk of 15% was to found to be the threshold at which statin therapy was cost saving for the NHS and it would have been appropriate to have assessed 15% risk level regardless of diabetes status as part of the assessment.

For secondary prevention Ezetimibe was only recommended for those in whom a statin is inappropriate and not tolerated and those patients who are able to tolerate only small dosages of statins insufficient to achieve satisfactory reduction of LDL or non HDL cholesterol does were not considered. In the 2007 version Ezetimibe therapy was

recommended as an option treatment for those in whom LDL cholesterol as not appropriately controlled because dose titration is limited by intolerance to initial statin therapy (Section 1.3 2007). This recommendation is particularly relevant and important in patients with familial hypercholesterolemia in whom CG71 recommends achievement of greater than 50% reduction LDL cholesterol and in whom Ezetimibe required to achieve satisfactory control.

In CG181 satisfactory of non HDL cholesterol is defined as achievement of greater that 40% reduction in non HDL cholesterol, equivalent to high intensity statin therapy, but this is non referred to anywhere in the document. As the Ezetimibe reduces HDL and non HDL by 15 – 20% the risk reduction will of course be dependent on the pre-treatment non HDL or LDL cholesterol or in statin treated, patients the non HDL or LDL cholesterol achieved after statin treatment. Those with higher non HDL and LDL cholesterol will have greater absolute benefit, and this should be taken into account cost effectiveness analysis. The previous document used baseline pre-treatment LDL cholesterol of 3.5 mmol/L as a basis of the modelling, but a sensitivity analysis with values above and below this could have been included. As some patients have a better response that others, this sensitivity analysis could inform decisions as to whether or not to persist with therapy after initial review of response.

2. Section 2: The Technology

Section 2 (Section 3 in the original 2007 version) which includes description of the licence indication (Section 2.2) longer refers the use of Ezetimibe in people with homozygous sitosterolaemia and in combination with statin in people with homozygous familial hypercholesterolemia. Although these latter indications may not be covered by this appraisal this should be referred to as previously under the description of licence indications.

3. Section 3

In the previous document section 3 was entitled Evidence and Interpretation which is much more appropriate.

4. Section 4

As a recommended in CG 181 assessment of cardiovascular risk of primary invention using QRISK2 should not be applied to patients with chronic kidney disease familial hypercholesterolemia or type 1 diabetes, it does not make sense to discriminate between patients with or without type 2 diabetes who are at similar cardiovascular risk.
Cardiovascular risk thresholds of 10% and 15% should have been modelled demonstrate appropriateness of selection 20% cardiovascular risk rather than altering selection based on the initial analysis of ERG.

In Section 4.17 the recommendation against using Ezetimibe as a second line therapy in secondary prevention conflicts with clinical evidence and current clinical practice as many patients fail to achieve satisfactory control of LDL/non HDL cholesterol (defined as greater than 40% reduction of non HDL cholesterol, equivalent of high intensity statin therapy).

Patients with established cardiovascular disease with acute coronary syndrome are at higher risk than those with stable coronary disease and should have been considered as separate sub group. As stated in CG71 and CG18, patients with CKD are very high risk of cardiovascular disease and are also susceptible to statin related muscle and renal toxicity. There is extensive safety and efficacy data for Ezetimibe in this group of patients and they are excluded from risk assessment with QRISK2 they should have been specified as a sub group and that could be offered ezetimibe alone or in combination with low dose statins.
In patients with familial hypercholesterolemia Ezetimibe in combination with highest tolerated statin dosage represents current standard of care in those patients failing to achieve satisfactory control of LDL-C (defined in CG71 as is greater than 50% reduction of LDL cholesterol). The only available alternative treatments are LDL apheresis (recommended for

those with aggressive coronary artery disease in CGG71). These groups should be acknowledged in the guideline and referred to recommendations in CG71 which is soon to be revised.

Overall, this guidance falls well short of standards we have come to expect from NICE Technology appraisals and extensive revision be required before this can be implemented clinical practice.

Response to the Single Technology Appraisal (STA) - Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (review of TA132) [ID627]

Respondent: Dr Adie Viljoen

Thank you for the opportunity to respond. I would like to make three main points:

1. Familial Hypercholesterolaemia (FH) was not mentioned in the draft document and the use of Ezetimibe in this population is not supported by the draft document. The majority of patients with FH are treated with statin together with Ezetimibe. Please note that this group cannot be placed in the primary prevention category. I tried to make this clear at the time of our meeting.

   CG71 refers to the place of Ezetimibe in treating this population. The recommendation for a 50% reduction of LDL-cholesterol and this document should be aligned such that the CG71 guidelines and QS41 (please see appendix below) are not incongruent. This is not routinely possible with statin monotherapy

   I propose including the use of Ezetimibe in combination with statin therapy or in monotherapy (in statin intolerant patients) as an option for patients with FH.

2. The use of CTT data for modelling purposes uses the best available data and this clearly shows the benefit of LDL-cholesterol reduction by statins which is similarly confirmed by the IMPROVE-IT trail data. The fact that the IMPROVE-IT trail falls on the CTT line confirms the LDL-cholesterol hypothesis and depicted by the IMPROVE-IT paper (see figure 1 below). Our understanding of LDL-cholesterol and the fundamental role it plays in the atherosclerosis process as well as the fact that intervention by reducing it is beneficial, is now stronger than ever before.

   I propose the extrapolation of the LDL-cholesterol data.

3. Importantly high risk patients for secondary prevention (e.g. patients a history of Acute Coronary Syndrome [ACS]) will only receive a statin and no additional treatment if this draft is not changed to incorporate the treatment of high risk group with a stain plus Ezetimibe (as suggested in TA132). This will lead to substantial under-treatment thus exposing these high risk patients to unjustifiable excess cardiovascular risk. Furthermore even higher risk patients won't receive any additional treatment either (e.g. patients with ACS plus diabetes or patients with two events).

   I propose the use of statin plus Ezetimibe in secondary prevention if the LDL-cholesterol is at a level where this is deemed cost-effective. Importantly, it was shown to be beneficial (i.e. reduce the composite endpoint) when the LDL-cholesterol reduced from 1.8 to 1.35 mmol/l by the addition of Ezetimibe in the post ASC population (IMPROVE-IT study).

Appendix

Figure 1.

IMROVE-IT on CTT line – NEJM June 2015

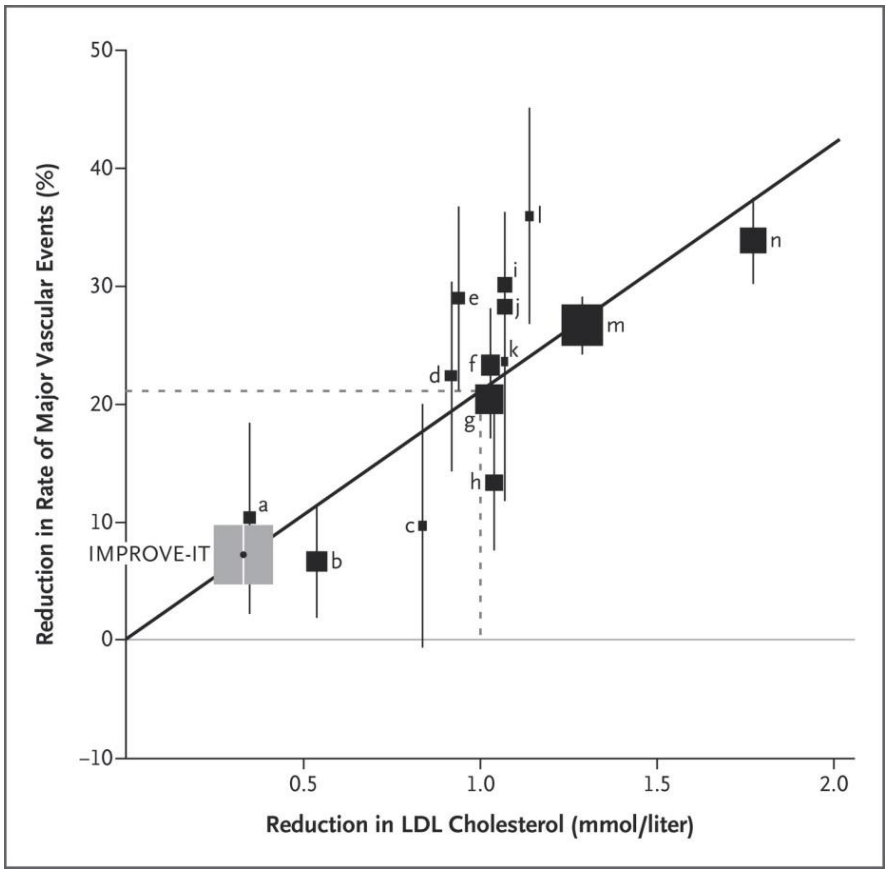
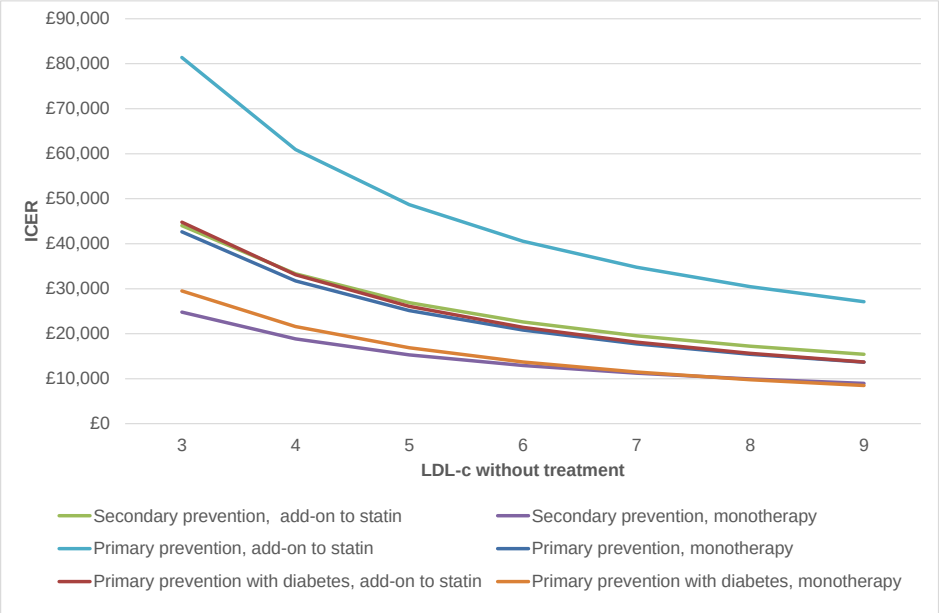


Figure 2.

ICER, baseline risk and LDL-cholesterol



Identification and management of familial hypercholesterolaemia

NICE guidelines [CG71] Published date: August 2008

1.3.1.3 Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

1.3.1.4 The dose of statin should be increased to the maximum licensed or tolerated dose to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

1.3.1.8 Ezetimibe, coadministered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-familial hypercholesterolaemia who have been initiated on statin therapy when[3]:

- serum total or LDL-C concentration is not appropriately controlled (as defined in recommendation 1.3.1.10) either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy (as defined in recommendation 1.3.1.11)

  and

- consideration is being given to changing from initial statin therapy to an alternative statin.

1.3.1.9 When the decision has been made to treat with ezetimibe coadministered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost[2].

1.3.1.10 For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk assessment in accordance with national guidance on the management of cardiovascular disease for the relevant populations

I have considered the Appraisal Committee's key conclusions on the use of ezetimibe in for treating primary heterozygous-familial and non-familial hypercholesterolaemia. I understand that the decision to recommend ezetimibe monotherapy for primary prevention who have both type 2 diabetes mellitus and a 20% or greater 10 year cardiovascular risk based on QALY gained. However clinically it is going to be difficult to manage patients without type 2 diabetes who have a high CV risk (20% or higher) and who are intolerant of statins. Currently these patients are offered ezetimibe. Without ezetimibe the therapeutic options for these patients are limited and include fibrates (with limited clinical evidence of effectiveness in terms of CV risk reduction) and nicotinic acid and its derivatives (which are poorly tolerated).

Prof Anne-Marie Kelly

Consultant Chemical Pathologist

Representing RCPath

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Cardiologist
Organisation	
Location	England
Conflict	No
Notes	I have attended advisory boards for MSD about Ezetimibe
Comments on individual sections of the ACD: I'm astonished by the provisional recommendations made. It is absolutely clear from the literature that LDL reduction is the driver behind CV risk reduction. Therefore the baseline level of LDL is a key determinant of the level of CV risk reduction from ezetimibe. It is obsurd to me to base QALY calculation on the absolute reduction of LDL just from the IMPROVE-IT study, as this was a study confined to patients already with low cholesterol levels (hence the reason why it was so hard to recruit patients to in the UK!). It would seem negligent of me as a clinician to withold this drug to someone who was at high risk - if they were either limited in statin dose due to side effects and still had high LDL, or with co-morbiditiies that mean statin treatment alone leaves them at risk of CV events. Furthermore, why havent you discussed the fact that the drug is off patent very soon - thereby rendering the cost analysis at that point irrelevant?	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	NHS Professional
Other role	Consultant Chemical Pathologist
Organisation	
Location	England
Conflict	No
Notes	A significant number of patients with FH have problems with statins. There needs to be an alternative - and the cost of ezetimibe is far less than Questran which would be the treatment given if ezetimibe is made unavailable. It is also very relevant that the patent for ezetimibe expires

	soon.
Comments on individual sections of the ACD: The comments by the committee about the failure to carry out ezetimibe monotherapy vs placebo testing seem to disregard the ethics position that once 4S and other similar studies proved that cholesterol lowering was beneficial, it became impossible to ethically use a placebo group. Therefore, it it wrong to criticise the company for failure to provide this type of evidence. The only reasonable evidence that can be provided is therefore add-on data and the effectiveness of monotherapy has to be imputed from the LDL reduction vs CHD rate data.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	The reduction achieved by ezetimibe is noted to be only 0.43 mmol/L. However, this is an average figure achieved in a trial and on average half of a group will do better than the average. In the real world (as opposed to trial-land) when we add a drug on, we test to ensure that it is being effective - and therefore if it only adds a tiny amount of extra reduction we stop using it. Thus, for the patients I use ezetimibe in conjunction with a statin I would stop using ezetimibe if I only got a 0.4mmol improvement - On average I would expect more than 1 mmol to be what I see as the benefit from ezetimibe in patients on combination therapy. The LDL : disease risk regression line shows that this adds significant benefit.
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	NHS Professional
Other role	Consultant Chemical Pathologist
Organisation	
Location	England
Conflict	No
Notes	I have previously received research funding, honoraria and/or assistance with attending scientific meetings from all major lipid lowering companies, including Merck Sharp & Dohme.
Comments on individual sections of the ACD: I support the recommendation that Ezetimibe monotherapy should be an option for treating primary heterozygous-familial (FH) and non-familial hypercholesterolaemia in adults with type 2 diabetes and >=20% 10 yr CVD risk or in secondary prevention. However this excludes a specific group in whom such Ezetimibe monotherapy may be required, ie primary prevention in FH. In FH patients it is not appropriate to calculate their CVD risk and they are recognised as justifying cholesterol lowering on the basis of their significantly elevated LDLC level, in line with NICE CG71 and NICE FH pathway. These patients start off with a much higher cholesterol level than other primary prevention patients and, where statins are considered inappropriate or not	

tolerated, Ezetimibe at present would be the best option to consider, with some patients achieving large reductions (it should be noted that the variability in cholesterol response to Ezetimibe is wider than to an individual dose/brand of statin. The reduction quoted in metanalysis of approx. 20% in LDLC is the average; some patients will have a significantly bigger reduction, others smaller, and this can and should be assessed by measurement after the first month of treatment).

I do not support the total non-recommendation for use of Ezetimibe as an add on to statin therapy. The first group of patients in whom add on treatment may be required is heterozygous FH, in line with NICE guidance (as above). With much higher LDLC than in IMPROVE-IT, the ICERs will be considerably less than modelled. Particular attention also needs to be given to very high risk patients, for example those with vascular disease plus diabetes, who are at much higher risk and with higher cholesterol levels, despite maximally tolerated statin, than those in IMPROVE-IT; ICERs will again be less than those calculated.

I was disappointed to read that Ezetimibe was no longer regarded as being innovative or a step change in management. Although some new treatments for lowering cholesterol have recently become available, and others are likely to appear over the next few years, these will, or are likely to be, significantly more expensive than Ezetimibe. At the current time statins remain the mainstay of treatment for the vast majority of patients. In those who cannot tolerate any or sufficient statin or in whom LDLC remains high on maximum statin eg in FH, Ezetimibe remains a step change in management for some of these needy patients.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	[redacted]
Other role	Non-profit organisation representing scientists and clinicians
Organisation	European Atherosclerosis Society
Location	Europe
Conflict	No
Notes	
Comments on individual sections of the ACD:	

It is not clear to us how the possible role of ezetimibe in the treatment of ACS (and high risk people) was addressed.

It appears calculations were made by taking in account the absolute risk reduction demonstrated in the IMPROVE IT. We believe that this, although based on the published data, is not the population of patients to be most likely treated with ezetimibe.

We suggest to extrapolate the benefit to those patients with high LDL-cholesterol on the maximal tolerated dose of a statin. In these patients the absolute benefit will be much larger, which is likely to make the intervention much more effective, both in risk reduction and, as a consequence, in NNT. Laufs et al. published a very crude approach which may make more understandable our concerns.[Understanding IMPROVE-IT and the cardinal role of LDL-C lowering in CVD prevention. Laufs U, Descamps OS, Catapano AL, Packard CJ.; Eur Heart J. 2014 Aug 7;35(30):1996-2000. doi: 10.1093/eurheartj/ehu228. Epub 2014 Jun 10.]

Patients with genetically elevated cholesterol (FH) and with high LDL in spite of statin treatment will benefit, and you can probably model the system to find a possible LDL-cholesterol threshold at which the benefit is also financially viable.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	NHS Professional
Other role	Consultant in Chemical pathology & Metabolic Medicine
Organisation	West Midlands Lipid Forum
Location	England
Conflict	No
Notes	The Doctors of the West Midlands Lipid Forum have agreed to the above statement. Some of the doctors have recieved speaker fees for presentations to local health providers, which are of their own opinion and not related to, or vetted by the manufacturer of this technology prior to presentation.

Comments on individual sections of the ACD:
Dear Sir/Madam,

We welcome the opportunity to respond to the appraisal consultation document for ezetimibe.

We believe that the committee has failed to recognise that in routine clinical use, ezetimibe is added in given to patients with a much higher LDL cholesterol than that in the trials. The reduction of LDL in the trials is noted to be only 0.43 mmol/L, but this is an average figure in the IMPROVE-IT trial for reduction of LDL cholesterol in patients starting with already low LDL cholesterol. As this is an average figure, half of patients would achieve a reduction greater than this. It should also be noted that in routine clinical practice, when using ezetimibe in combination with a statin, the reduction in LDL cholesterol is usually observed to be approximately 1 mmol/L on average, which is much greater than the 0.43 mmol/L quoted. The IMPROVE IT therapeutic scenario is far removed from day to day clinical practice, where ezetimibe is prescribed to patients with high LDL cholesterol that cannot be controlled with statin monotherapy. The "lower is better" LDL cholesterol regression line shows that this adds significant benefit. Therefore, when interpreting the clinical benefit of ezetimibe, it is important to remember that the absolute risk reduction for the same relative LDL cholesterol lowering diminishes for the same relative LDL cholesterol lowering with lower baseline LDL cholesterol. (1) (See figure in paper) We believe it is therefore incorrect to base QALY calculations on the absolute reduction of LDL cholesterol from the IMPROVE IT trial data.

1 Understanding IMPROVE IT and the cardinal role for LDL-C lowering in CVD prevention, Laufs et al. EHJ 2015

We would also like to draw to the committee's attention to the American College of Cardiology / American Heart Association 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk: a new paradigm supported by more evidence, and the European Society of Cardiology 2015 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. (2,3) These guidelines are evidence based and both recommend the wider use of ezetimibe than NICE are suggesting. They both state that ezetimibe, when added to statin therapy, haves a role in cholesterol lowering and provides clinical benefit.

2. The 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk: a new paradigm supported by more evidence. Robinson JG, Stone NJ. EHJ 2015

3. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. EHJ 2015

The committee has also commented on the fact that there is a lack of evidence comparing ezetimibe monotherapy to placebo. This would not be possible to perform as it would be unethical to do this study; the 4S and other similar studies proved that cholesterol lowering is beneficial, and therefore it is impossible to use a placebo group ethically. Therefore, it is wrong to criticise the company for failure to provide this type of evidence. The only reasonable evidence that can be provided is therefore add-on data and the effectiveness of monotherapy has to be imputed from the LDL reduction vs CHD rate data.

We believe that NICE also need to be aware of tolerability of the recommended add on therapy that they are suggesting. If we are not to use ezetimibe as an add on therapy, in patients with high risk and those with heterozygous FH, we are left to use other, non-evidence based treatments. Ezetimibe is, on the whole, well tolerated by patients, whereas the bile acid sequestrants are less well tolerated and more expensive thatn ezetimibe, and therefore it is difficult to achieve a dose that patients can tolerate and achieve the lipid lowering effects required.

We believe it is wholly unethical to withhold ezetimibe from patients who remain at high risk, be that due to inability to tolerate high dose statins or where they have significant co morbidities.

The committee has also not taken into account the short period of time that ezetimibe has left on patent, meaning that the costs are likely to significantly decrease in 2018.

We believe that in line with the evidence and NICE CG 181, that ezetimibe should be used as add on therapy for those patients who are not to target with the LDL cholesterol, and as monotherapy for those with high cardiovascular risk, who are unable to tolerate statins.

Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Received by email

Dear Professor Longson,

I understand that NICE is in the process of producing new guidelines for the prescribing of Ezetimibe. Apparently comments from patients were due in by yesterday, 10th November, and I only found out about this today, having been on holiday for the past week.

I was recently in touch with a [redacted] from Newcastle who had asked if I would share my recent experience of Ezetimibe with his contact in Heart UK as that organisation has some input into the consultation process regarding this drug, and I will forward this message to him as well.

I am a [redacted] year old lady with hypercholesterolaemia who has taken Ezetimibe over an extended period. I had a lot of difficulty from July 2014 until September 2015 trying to get Ezetimibe represcribed as the local CCG, for the [redacted] GP practice I attend, was unwilling to let me go back on it despite me being intolerant of statins. I had had a long history of taking it almost since its introduction and it was effective. During the period from August 2013 to early 2014 after I stopped taking it my total cholesterol rose to over 8mmol/L and as I have a high level of Lp"a" - 130-150mgm/dL and am a heterozygote for Factor V Leiden, the lipid clinic I attend is keen for me to keep my LDLC as low as possible. I had a pulmonary embolism in March 2014 and the lipid clinic recommended I go back on the Ezetimibe to reduce the risk of any reoccurrence. It took until September this year to get it prescribed again and within 6 weeks my TC reduced from 7.6 to 5.4mmol/L with HDLC staying the same at 2.5mmol/L. (see attached graphs). This is over a 40% reduction in LDLC in a short time. Although my risk for cardiac events looking at Cholesterol and TG levels alone is not excessively high with a TC/HDLC usually well under 4 at its worst, when taken with the Lp"a" and Factor V Leiden, the lipid clinic thinks the normal way of evaluating risk underestimates my risk. The rapid response to Ezetimibe must indicate that I'm a cholesterol over-absorber rather than an overproducer however, the general prescribing of cholesterol lowering drugs, as far as I know, doesn't distinguish and testing isn't specific.

If I look on-line there seem to be numerous CCG's who are very reluctant to allow prescribing of Ezetimibe and this concerns me. How many other patients are out there who might benefit, if it does translate into a reduction of cardiac events. It was mentioned to me that it is becoming clearer that those patients with a high TC but also high HDLC and low TGs don't do well on statins, but I don't know whether there have been any trials done yet that show that.

I hope the above isn't too late to be included in the discussion.

Kind regards,

[redacted]