NICE National Institute for Health and Care Excellence

NICE guidance

Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia

Technology appraisal guidance
Published: 24 February 2016

www.nice.org.uk/guidance/ta385

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA132.

This guidance is the basis of QS100.

1 Recommendations

1.1 This guidance should be used with NICE's guidelines on cardiovascular disease: risk assessment and reduction, including lipid modification and familial hypercholesterolaemia: identification and management.

1.2 Ezetimibe monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults in whom initial statin therapy is contraindicated.

1.3 Ezetimibe monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who cannot tolerate statin therapy (as defined in section 1.6).

1.4 Ezetimibe, co-administered with initial statin therapy, is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who have started statin therapy when:

- serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled (as defined in section 1.7) 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 section 1.6) **and**
- a change from initial statin therapy to an alternative statin is being considered.

1.5 When prescribing ezetimibe co-administered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.

1.6 For the purposes of this guidance, intolerance to initial statin therapy is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.

1.7 For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individual risk assessment according to national guidance on managing cardiovascular disease in the relevant populations.

2 The technology

2.1 Ezetimibe (Ezetrol, Merck Sharp & Dohme) is a cholesterol-absorption inhibitor that blocks the intestinal absorption of dietary and biliary cholesterol and related plant sterols, without affecting the uptake of triglycerides or fat-soluble vitamins. Because of this mechanism of action, ezetimibe can be combined with a statin to provide either a complementary or an alternative mode of cholesterol reduction.

2.2 Ezetimibe, with a statin or as monotherapy, has a marketing authorisation in the UK. It is licensed in combination with an HMG-CoA reductase inhibitor (statin) as an adjunctive therapy to diet for primary heterozygous-familial or non-familial hypercholesterolaemia that is not appropriately controlled with a statin alone. Ezetimibe monotherapy has a marketing authorisation as an adjunctive therapy to diet for primary heterozygous-familial or non-familial hypercholesterolaemia when a statin is considered inappropriate or is not tolerated.

2.3 Adverse reactions with ezetimibe as monotherapy or with a statin are usually mild and transient. When given as monotherapy, they most commonly include abdominal pain, diarrhoea, flatulence and fatigue. When taken with a statin, the most common additional adverse reactions include increased alanine transaminase, aspartate transaminase or both, headache and myalgia. For full details of adverse effects and contraindications, see the summaries of product characteristics.

2.4 Ezetimibe is taken orally at a dose of 10 mg once daily. Ezetimibe is available as 10-mg tablets (28-tablet pack) at a net price per pack of £26.31 (excluding VAT; BNF, accessed September 2015). A fixed-dose combination tablet (Inegy, Merck Sharp & Dohme) containing ezetimibe 10 mg and simvastatin 20 mg (28-tablet pack) is available at a net price per pack of £33.42, ezetimibe 10 mg and simvastatin 40 mg (28-tablet pack) at a net price per pack of £38.98, and ezetimibe 10 mg and simvastatin 80 mg (28-tablet pack) at a net price per pack of £41.21 (excluding VAT; BNF; accessed September 2015). Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

The appraisal committee considered evidence submitted by consultees, Merck Sharp & Dohme and a review of this submission by the evidence review group (ERG). This appraisal was a review of the original NICE technology appraisal guidance on ezetimibe that published as TA132 in 2007. The review focused on the cardiovascular outcome data from IMPROVE-IT, a study done since the original guidance was published.

Clinical effectiveness

3.1 IMPROVE-IT was a randomised, double-blind, active-controlled study in 18,144 patients with stabilised acute coronary syndrome. Patients were randomised in a 1:1 ratio to either ezetimibe 10 mg plus simvastatin 40 mg once daily or simvastatin 40 mg once daily. At a median follow-up of 6 years, ezetimibe plus simvastatin produced a 6.4% relative risk (RR) reduction in the primary composite efficacy end point of cardiovascular death, major coronary event, or non-fatal stroke compared with simvastatin alone (hazard ratio [HR] 0.936, 95% confidence interval [CI] 0.89 to 0.99). There was a reduction in low-density lipoprotein cholesterol at 1 year of 0.43 mmol/litre with ezetimibe plus simvastatin compared with simvastatin alone (a relative reduction of 24%). The company reported that no new safety concerns related to ezetimibe were raised in IMPROVE-IT.

3.2 The company submitted evidence suggesting that clinical outcomes from IMPROVE-IT were consistent with a large Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of statins. The evidence showed that a 1 mmol/litre reduction in LDL cholesterol from IMPROVE-IT had a similar hazard ratio for cardiovascular events (HR 0.80, 95% CI 0.68 to 0.94) to the CTTC analysis (HR 0.78, 95% CI 0.76 to 0.80).

Cost effectiveness

3.3 The company submitted a Markov model based on the modelling approaches previously developed for NICE's technology appraisal guidance on statins for the

prevention of cardiovascular events and its original guidance on ezetimibe. NICE's original technology appraisal guidance on ezetimibe presented base-case results for people who could tolerate statins and people in whom statins were contraindicated or not tolerated. But to be consistent with the updated NICE guideline on lipid modification, the company presented base-case results for the primary and secondary prevention of cardiovascular disease instead of the populations as in the original appraisal.

3.4 In NICE's original technology appraisal guidance on ezetimibe, the CTTC meta-analysis was used to model treatment effect by linking the absolute reduction in LDL cholesterol to the proportional reduction in cardiovascular events. Although IMPROVE-IT subsequently investigated the effect of adding ezetimibe to statin therapy on reducing cardiovascular events, the patient population was narrower than that specified in ezetimibe's marketing authorisation. Therefore, the company decided not to use the IMPROVE-IT data in its economic model. Instead, it chose to use the CTTC meta-analysis to model the effect of ezetimibe on cardiovascular outcomes linked to decreased LDL cholesterol.

4 Committee discussion

4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of ezetimibe, having considered evidence on the nature of primary heterozygous-familial and non-familial hypercholesterolaemia and the value placed on the benefits of ezetimibe by people with the conditions, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.2 This appraisal is a review of the original NICE technology appraisal guidance on ezetimibe. The committee noted that ezetimibe monotherapy was recommended as an option for treating primary hypercholesterolaemia in adults who:

- are unable to start statin therapy because it is contraindicated
- cannot tolerate statin therapy.

It noted that ezetimibe, co-administered with initial statin therapy, was recommended as an option for treating primary hypercholesterolaemia in adults when:

- they have started statin therapy and low-density lipoprotein (LDL) cholesterol is not appropriately controlled either after dose titration of initial statin therapy or because dose titration is limited by intolerance to statin therapy and
- changing to an alternative statin is being considered.

The committee was aware that NICE's guideline on lipid modification cross-referred to NICE's technology appraisal guidance on ezetimibe.

Current practice and treatment

4.3 The committee considered current NHS practice for treating primary hypercholesterolaemia. The committee observed that the patient population in

the company's submission was different to the population covered by the marketing authorisation and the final NICE scope for ezetimibe (see section 2.2). This was because the company's submission considered a primary prevention population (people with a 10-year risk of developing cardiovascular disease of 10% to 30%) and a secondary prevention population (people with established cardiovascular disease) with primary heterozygous-familial or non-familial hypercholesterolaemia. It noted that this was because the updated NICE guideline on lipid modification made recommendations according to primary and secondary prevention of cardiovascular risk. The committee heard from the clinical experts and noted the comments received at consultation that suggested the way cardiovascular risk is assessed and managed may have changed since the original NICE technology appraisal guidance on ezetimibe was published. It further heard that despite the recommendations in NICE's guideline on lipid modification, which are largely based on assessing 10-year cardiovascular risk using the cardiovascular disease risk calculator QRISK2, meeting target cholesterol levels to prevent cardiovascular disease remained an important part of clinical practice in England. The committee concluded that, in clinical practice in the NHS in England, treating hypercholesterolaemia to prevent cardiovascular disease starts either because of a person's 10-year risk of developing cardiovascular disease or to meet a specific target cholesterol level. The committee further concluded that this remained consistent with the approach taken in NICE's original technology appraisal guidance on ezetimibe.

4.4 The committee considered the current treatment pathway for people with primary hypercholesterolaemia. The committee heard from the clinical experts that statins are the main treatment for familial and non-familial hypercholesterolaemia (as described in NICE's guidelines on familial hypercholesterolaemia and on lipid modification). It further heard from the clinical experts that fibrates, nicotinic acid and bile acid sequestrants (anion exchange resins) are not routinely used to treat non-familial hypercholesterolaemia. The committee then heard that, although recommended in NICE's guideline on familial hypercholesterolaemia, these treatments are not commonly used to treat familial hypercholesterolaemia because they are poorly tolerated. It heard from the clinical experts that ezetimibe monotherapy is used to treat primary hypercholesterolaemia when a statin is considered inappropriate or is not tolerated; ezetimibe with a statin is used in people when cholesterol levels are not low enough, despite increasing the dose of the statin, or if a person is unable

to have higher doses of the statin because it is likely to cause side effects. The committee concluded that statins are the main option for treating primary hypercholesterolaemia (when a statin is considered appropriate), and that no treatments apart from ezetimibe monotherapy are established NHS practice in England for treating familial and non-familial hypercholesterolaemia in adults who are unable to take a statin.

Clinical effectiveness

4.5 The committee discussed the clinical effectiveness of ezetimibe, focusing on the relevance of the new evidence from IMPROVE-IT in reducing cardiovascular events in people with primary hypercholesterolaemia. The committee heard from the clinical experts and noted consultation comments that stated the IMPROVE-IT population represented only part of the eligible population who could have statins or ezetimibe. This was because the patients in IMPROVE-IT had acute coronary syndrome (that is, they were having treatment for secondary prevention, and not primary prevention, of cardiovascular disease). It noted the comments made by consultees that although IMPROVE-IT's lower baseline LDL cholesterol level resulted in a smaller absolute reduction in LDL cholesterol with ezetimibe compared with the wider secondary prevention population, it considered this to be consistent with the trend predicted by the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis (see section 3.2). The committee considered that ezetimibe plus a statin was more clinically effective than a statin alone in IMPROVE-IT, as shown by lower LDL cholesterol and reduced cardiovascular events, but agreed that the trial population was not wholly representative of the population receiving ezetimibe in current NHS practice in England. The committee recalled that the original NICE technology appraisal guidance on ezetimibe concluded that ezetimibe co-administered with a statin was clinically effective in adults in whom primary hypercholesterolaemia was not appropriately controlled with statin therapy compared with statins. It also recalled that ezetimibe monotherapy was clinically effective compared with placebo in people for whom statins were contraindicated or who cannot tolerate them. The committee therefore decided that the clinical effectiveness of ezetimibe using the updated evidence base was consistent with that in NICE's original technology appraisal guidance on ezetimibe, and that the conclusions it had previously made were still appropriate.

Cost effectiveness

4.6 The committee considered the cost effectiveness of ezetimibe following the comments received at consultation. The committee noted that some consultees preferred the original cost effectiveness analyses and recommendations for ezetimibe, which did not differentiate between primary and secondary prevention of cardiovascular disease when treating hypercholesterolaemia or use results from IMPROVE-IT. The committee decided that the company's current incremental cost-effectiveness ratios (ICERs) according to primary and secondary prevention of cardiovascular disease and the evidence review group's (ERG's) estimates using IMPROVE-IT were not suitable for decision making. The committee considered the estimated ICERs from the original appraisal of ezetimibe to be more plausible than the current estimates from the company and ERG because the population in the original appraisal was better aligned with the final NICE scope, current practice and ezetimibe's marketing authorisation. The committee concluded that current practice, treatment (see sections 4.3 and 4.4) and the clinical effectiveness of ezetimibe using the updated evidence base (see section 4.5) are consistent with NICE's original technology appraisal guidance. Therefore, the cost effectiveness of ezetimibe was likely to be more plausible in NICE's original technology appraisal guidance compared with the current estimates from the company and the ERG. It decided not to use the company and ERG's current cost-effectiveness estimates for ezetimibe for its decision making. It further concluded that the recommendations in NICE's original technology appraisal guidance on ezetimibe were still appropriate (see section 4.2). The committee agreed to amend the recommendations so that they no longer referred to superseded NICE guidance.

4.7 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of ezetimibe in this appraisal.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 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 healthcare professional responsible for their care thinks that ezetimibe is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal committee members and NICE project team

Appraisal committee members

The appraisal committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the committee members who took part in the discussions for this appraisal appears below. There are 4 appraisal committees, each with a chair and vice chair. Each appraisal committee meets once a month, except in December when there are no meetings. Each committee considers its own list of technologies, and ongoing topics are not moved between committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Professor Kathryn Abel
Institute of Brain and Behaviour Mental Health, University of Manchester

Mr David Chandler
Lay Member

Mrs Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Department of Primary Care and Population Health, University College London

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Nigel Langford
Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Dr Patrick McKiernan
Consultant Pediatrician, Birmingham Children's Hospital

Dr Iain Miller
Founder and Chief Executive Officer, Health Strategies Group

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Dr Anna O'Neill
Deputy Head of Nursing and Health Care School, Senior Clinical University Teacher, University of Glasgow

Professor Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Dr Paul Tappenden
Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry

Dr Judith Wardle
Lay Member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Jasdeep Hayre
Technical Lead

Linda Landells
Technical Adviser

Lori Farrar
Project Manager

7 Sources of evidence considered by the committee

The evidence review group (ERG) report for this appraisal was prepared by Aberdeen Health Technology Assessment (HTA) Group:

- Scotland G, Javanbakht M, Scott N et al. Ezetimibe for treating primary (heterozygous-familial and non-familial) hypercholesterolaemia. Aberdeen HTA Group, August 2015

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Companies or sponsors were also invited to make written submissions. Professional or expert, patient or carer groups, and other consultees had the opportunity to make written submissions. Companies or sponsors, professional or expert, patient or carer groups, and other consultees also have the opportunity to appeal against the final appraisal determination.

Company or sponsor:

- Merck Sharp & Dohme Ltd

Professional or expert, and patient or carer groups:

- HEART UK
- British Heart Foundation
- Royal College of Pathologists
- Royal College of Physicians

Other consultees:

- Department of Health
- NHS England
- NHS Oxfordshire Clinical Commissioning Group

- NHS West Essex Clinical Commissioning Group
- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Aberdeen Health Technology Assessment Group
- National Institute for Health Research Health Technology Assessment Programme

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia by attending the initial committee discussion and providing a written statement to the committee. They were also invited to comment on the ACD.

- Dr Adie Viljoen, Chemical Pathologist, nominated by Merck Sharp & Dohme Ltd – clinical expert
- Professor Anne-Marie Kelly, Consultant Chemical Pathologist, nominated by the Royal College of Pathologists – clinical expert
- Stephen Boley, nominated by HEART UK – patient expert

Representatives from the following company attended committee meetings. They contributed only when asked by the committee chair to clarify specific issues and comment on factual accuracy.

- Merck Sharp & Dohme Ltd

ISBN: 978-1-4731-1706-8