Ezetimibe and simvastatin (Inegy) for reduction of cardiovascular risk in coronary heart disease

SUMMARY

This product is a fixed dose combination of ezetimibe and simvastatin. It is intended for the reduction of cardiovascular risk (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or need for revascularisation) in patients with coronary heart disease - not appropriately controlled with a statin alone or not already receiving lipid lowering therapy. If licensed, a fixed dose combination of ezetimibe and simvastatin will offer an alternative treatment option for this patient group. Ezetimibe is a cholesterol-absorption inhibitor that is thought to act by blocking Niemann-Pick C1-like-1 protein, a critical molecule for intestinal cholesterol absorption, whereas simvastatin decreases endogenous liver production of cholesterol by inhibiting HMG-CoA reductase.

Diseases of the heart and circulatory system (cardiovascular disease or CVD) are the most common cause of death in the UK accounting for almost 191,000 deaths each year – one in three of all deaths. The main forms of CVD are CHD and stroke. The prevalence of CVD in the UK increases with age and is higher in men than in women. There are over 1.6 million men and over 1 million women in the UK with CHD, giving a total of nearly 2.7 million people. Nearly 1.6 million of these people are less than 75 years of age. In 2011-12, there were 282,569 admissions for coronary heart disease in England, resulting in 1,163,109 bed-days and 409,508 finished consultant episodes. 64,435 deaths were registered in England and Wales during 2011.

Treatment of CHD aims to prevent recurrent cardiovascular events by reducing individual patients’ cardiovascular risk. This includes lifestyle changes such as dietary modification, smoking cessation, and exercise. Current pharmacological treatment options for the prevention of cardiovascular events in high-risk patients include lipid lowering therapies, antiplatelet therapy and antihypertensive therapy. Ezetimibe/simvastatin is currently in one phase III trial comparing its effect on time to first occurrence of major adverse cardiovascular event against treatment with simvastatin alone. This trial is expected to complete in September 2014.
**TARGET GROUP**

- Reduction of cardiovascular risk in patients with coronary heart disease (CHD).

**TECHNOLOGY**

**DESCRIPTION**

This product is a fixed dose combination of ezetimibe and simvastatin (Inegy, MK-0653A). Ezetimibe is a cholesterol-absorption inhibitor that is thought to act by blocking Niemann-Pick C1-like-1 protein, a critical molecule for intestinal cholesterol absorption, whereas simvastatin decreases endogenous liver production of cholesterol by inhibiting HMG-CoA reductase. The combination of these two different cholesterol-lowering mechanisms may achieve an additive or synergistic cholesterol-lowering effect. Ezetimibe/simvastatin is intended for the reduction of cardiovascular risk (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or need for revascularisation) in patients with CHD - not appropriately controlled with a statin alone or not already receiving lipid lowering therapy. In the phase III clinical trial, ezetimibie/simvastatin fixed dose combination is administered at 10/40mg once daily.

Ezetimibe/simvastatin (Inegy) is licensed in the UK for the treatment of:

- Primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where patients are not appropriately controlled with a statin alone or where patients have already been treated with a statin and ezetimibe. Adjunctive therapy to diet.
- Homozygous familial hypercholesterolaemia (HoFH). Adjunctive therapy to diet.

The most frequent treatment-related adverse events (AEs) associated with ezetimibe/simvastatin when used for its licensed indication include: an increase in liver enzymes (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]), increase in blood creatinine kinase (CK) and myalgia.

**INNOVATION and/or ADVANTAGES**

If licensed, a fixed dose combination of ezetimibe and simvastatin will offer an alternative treatment option for this patient group.

**DEVELOPER**

Merck Sharp & Dohme Ltd (MSD).

**AVAILABILITY, LAUNCH OR MARKETING**

In phase III clinical trials.
The accumulation of low density lipoprotein (LDL) cholesterol in the intima (inner lining) of arteries and associated inflammatory reactions gradually lead to the formation of atherosclerotic plaques within the arterial tree. Atherosclerotic plaques in the coronary arteries obstruct blood flow and reduce oxygen supply to the myocardium, which in turn produces the typical symptom of CHD, chest pain (angina pectoris). Other symptoms include exertional dyspnoea and fatigue, arrhythmias, and heart failure. Chronic stable angina and acute coronary syndrome (ACS) are clinical manifestations of CHD. ACS refers to a spectrum of clinical presentations, ranging from ST-segment elevation myocardial infarction (STEMI) to presentations found in non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). The key behavioural risk factors for CHD include smoking, physically inactive lifestyles, poor diet, excess salt, obesity and alcohol consumption. Medical risk factors include high blood pressure, high blood cholesterol, being overweight and obese, and diabetes.

This topic is relevant to the National Service Framework for coronary heart disease (2005).

Diseases of the heart and circulatory system (cardiovascular disease or CVD) are the most common cause of death in the UK accounting for almost 191,000 deaths each year – one in three of all deaths. The main forms of CVD are CHD and stroke. The prevalence of CVD in the UK increases with age and is higher in men than in women. There are over 1.6 million men and over 1 million women in the UK with CHD, giving a total of nearly 2.7 million people. Nearly 1.6 million of these people are less than 75 years of age.

An estimated 233,600 people are diagnosed with acute coronary syndrome (ACS) annually in the UK. The overall prevalence of angina (stable and unstable) in the UK is approximately 5% in men and 4% in women (8% of men and 3% of women aged 55 to 64 years and about 14% of men and 8% of women aged 65 to 74 years). It is estimated that there are around 1.5 million people who have previously suffered a myocardial infarction in the UK, and nearly 600,000 individuals of each sex who have had a stroke. Risk of CHD is directly related to blood cholesterol levels. It is estimated that around 60% of CHD is due to increased total blood cholesterol levels. The proportion of people with high cholesterol (total cholesterol levels of 5mmol/l and over) in England ranges between 54% and 64% for men and 56% and 68% for women.

In 2010-11, there were 282,569 admissions for atherosclerotic heart disease (ICD-10 I20-I25) in England, resulting in 1,163,109 bed-days and 409,508 finished consultant episodes. 64,435 deaths were registered in England and Wales during 2011. CVD is estimated to cost the UK economy around £30bn a year.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal. Ticagrelor for the treatment of acute coronary syndromes (TA236). October 2011
- NICE technology appraisal. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (TA210). December 2010
- NICE technology appraisal. Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (TA132). August 2010
- NICE technology appraisal. Statins for the prevention of cardiovascular events (TA94). November 2008
- NICE clinical guideline. Unstable angina and NSTEMI (CG94). March 2010
- NICE clinical guideline. Type 2 diabetes: the management of type 2 diabetes (CG87). May 2009

Other Guidance

- European Society of Cardiology and the European Atherosclerosis Society. ESC/EAS guidelines for the management of dyslipidaemias. 2011
EXISTING COMPARATORS and TREATMENTS

Treatment of CHD aims to prevent recurrent cardiovascular events by reducing CHD patients' cardiovascular risk, which includes lifestyle changes such as dietary modification, smoking cessation, and exercise. Current pharmacological treatment options for the prevention of cardiovascular events in high-risk patients include\(^5,24,26\):

- Lipid lowering therapies, which include statins (simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin), fibrates (bezafibrate, ciprofibrate, fenofibrate and gemfibrozil), nicotinic acid and anion exchange resins.
- Antiplatelet therapy: aspirin, clopidogrel,prasugrel, ticagrelor,abciximab, eptifibatide, tirofiban.
- Antihypertensive therapy which include, ACE inhibitors, angiotensin-II receptor antagonists, thiazides and calcium channel blockers.
- Beta blockers such as propranolol, timolol and metoprolol.

Current guidelines may also recommend revascularisation procedures in appropriate patients\(^3\):
- Percutaneous coronary intervention (PCI) angioplasty with stent placement.
- Coronary artery bypass grafting (CABG).

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>IMPROVE-IT, NCT00202878, P04103; ezetimibe/simvastatin vs simvastatin alone; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Merck Sharp &amp; Dohme Corp., a subsidiary of Merck &amp; Co. Inc.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Publication(^2/), trial registry(^29).</td>
</tr>
<tr>
<td>Location</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=18,141 (planned); 18 years and older; within 10 days of admission for ACS; clinically stable.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to ezetimibe/simvastatin 10/40mg oral, once daily; or simvastatin 40mg oral, once daily.</td>
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<tr>
<td>Follow-up</td>
<td>Follow-up minimum 2.5 years.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>CV death, non-fatal MI, hospital admission for unstable angina, non-fatal stroke.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Death due to any cause, major coronary event, or non-fatal stroke; CHD death, urgent coronary revascularisation with either PCI or CABG occurring at least 30 days after randomisation.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Primary completion date reported as Sept 2014.</td>
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ESTIMATED COST and IMPACT

COST

The cost of ezetimibe/simvastatin has not yet been determined for this indication. However, this product is already marketed in the UK; a pack of 28 x 10/40mg tablets costs £38.98\(^{29}\).
IMPACT - SPECULATIVE

Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: improved patient convenience (single tablet daily)
- No impact identified

Impact on Services
- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- None identified

Impact on Costs
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- None identified

Other Issues
- Clinical uncertainty or other research question identified
- None identified

REFERENCES

20 European Society of Cardiology. ESC/EAS Guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). European Heart Journal 2011;32:1769-1818.