LCZ696 for chronic heart failure – first line

SUMMARY

LCZ696 is an orally active angiotensin receptor neprilysin inhibitor (ARNI). It is intended as first line treatment for patients with chronic heart failure (NYHA stage II-IV) and reduced left ventricular ejection fraction and is administered orally at 200mg twice daily.

Heart failure is a complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart as a pump is impaired. It is caused by structural or functional abnormalities of the heart – often because the myocardium has become too weak or stiff to function efficiently. Breathlessness, fatigue and fluid retention (oedema) are the main symptoms of chronic heart failure. The three main types of chronic heart failure are: (1) heart failure due to left ventricular systolic dysfunction (associated with a reduced left ventricular ejection fraction), (2) heart failure with preserved ejection fraction, and (3) heart failure due to valve disease. Key causes for the development of chronic heart failure include: hypertension, coronary heart disease, atrial fibrillation, heart valve disease and chronic alcohol misuse.

Approximately 900,000 people in the UK have heart failure. Almost as many people have impaired cardiac function – but as yet, no symptoms of heart failure. More than 395,240 patients registered with general practitioners in England were diagnosed with this condition between April 2011 and March 2012, an unadjusted prevalence of 0.7% of all patients registered. In England in 2011-12, there were 61,130 admissions for heart failure accounting for approximately 2% of all NHS inpatient bed days and 5% of all emergency medical admissions to hospital. In 2010, heart failure accounted for 5,378 deaths in England, though death figures are widely acknowledged to be underestimated.

LCZ696 is currently in a phase III clinical trial comparing its effect on time to death (cardiovascular cause) or hospitalisation for heart failure against treatment with enalapril.
TARGET GROUP

- Chronic heart failure: NYHA\textsuperscript{a} II-IV; patients with reduced left ventricular ejection fraction (LVEF) <40% – first line.

TECHNOLOGY

DESCRIPTION

LCZ696 is an orally active angiotensin receptor neprilysin inhibitor (ARNI). LCZ696 is intended as first line treatment for patients with chronic heart failure (NYHA stage II-IV) and reduced left ventricular ejection fraction (LVEF <40%) and is administered orally at 200mg twice daily.

LCZ696 is also in phase III development for hypertension.

INNOVATION and/or ADVANTAGES

LCZ696 is a first in class agent and if licensed, will offer an additional treatment option for this patient group. The company claim LCZ696 has the potential to improve safety by avoiding side effects associated with inhibition of the major bradykinin-degrading pathway.

DEVELOPER

Novartis General Medicines.

AVAILABILITY, LAUNCH OR MARKETING

Currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Heart failure is a complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart as a pump is impaired\textsuperscript{1}. It is caused by structural or functional abnormalities of the heart – often because the myocardium has become too weak or stiff to function efficiently\textsuperscript{1,2}. Breathlessness, fatigue and fluid retention (oedema) are the main symptoms of chronic heart failure. The liver may also become enlarged and sufferers may experience more general symptoms such as: dizziness, nausea, constipation and loss of appetite\textsuperscript{3}.

There are three main types of chronic heart failure\textsuperscript{1,2}:

- heart failure due to left ventricular systolic dysfunction – due to left ventricular weakness and associated with a reduced LVEF.

\textsuperscript{a} NYHA: The New York Heart Association Functional Classification – places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees of shortness of breath and/or angina pain.
• heart failure with preserved ejection fraction – usually due to left ventricular stiffness, causing difficulty in filling with blood.
• heart failure due to valve disease.

Key causes for the development of chronic heart failure include: hypertension, coronary heart disease, atrial fibrillation, heart valve disease and chronic alcohol misuse\(^1\). Many patients with chronic heart failure have had a previous myocardial infarction\(^1\). Chronic heart failure has a major impact on longevity and quality of life\(^4\).

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to: The National Service Framework for Coronary Heart Disease (2000).

CLINICAL NEED and BURDEN OF DISEASE

Around 900,000 people in the UK have heart failure. Almost as many people have impaired cardiac function – but as yet, no symptoms of heart failure\(^3\). More than 395,240 patients registered with general practitioners in England were diagnosed with this condition between April 2011 and March 2012, an unadjusted prevalence of 0.7% of all patients registered\(^5\). In England, there were 61,130 admissions for heart failure (ICD10 I50) in 2011-12\(^6\) accounting for approximately 2% of all NHS inpatient bed days and 5% of all emergency medical admissions to hospital\(^7\). Heart failure has a poor prognosis – hospital readmissions are common: about 1 in 4 patients are readmitted within 3 months\(^7\) and 30–40% of patients diagnosed with heart failure die within a year\(^7\) (but thereafter the mortality is less than 10% per year)\(^7\). There is evidence of a trend of improved prognosis in the past ten years. The six-month mortality rate decreased from 26% in 1995 to 14% in 2005\(^1\). In 2010, heart failure (ICD10 I50) accounted for 5,378 deaths in England, though death figures are widely acknowledged to be underestimated\(^8\),\(^10\).

The population likely to be eligible to receive LCZ696 could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Arrhythmias – ICDs & Heart failure - cardiac resynchronisation [ID481]. Expected September 2013\(^11\).
- NICE technology appraisal. Ivabradine for treating chronic heart failure (TA267). November 2012\(^12\).
- NICE technology appraisal. Cardiac resynchronisation therapy for the treatment of heart failure (TA120). May 2007\(^13\).
- NICE technology appraisal. Implantable cardioverter defibrillators for arrhythmias (TA95). January 2006\(^14\).
- NICE interventional procedure guidance. Percutaneous mitral valve annuloplasty: guidance (IPG352). July 2010\(^15\).
• NICE interventional procedure guidance. Short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery (IPG177). June 2006\textsuperscript{16}.

Other Guidance

• European Society of Cardiology. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. May 2012\textsuperscript{17}.
• The BACPR Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation 2012\textsuperscript{18}.
• European Society of Cardiology. European Society of Cardiology Heart Failure Association Standards for delivering heart failure care. 2011\textsuperscript{19}.
• NHS Quality Improvement Scotland. Clinical Standards for Heart Disease. April 2010\textsuperscript{20}.
• Scottish Intercollegiate Guidelines Network. Management of chronic heart failure: a national clinical guideline CG95. 2007\textsuperscript{21}.
• ACC/AHA Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult. 2005\textsuperscript{22}.

EXISTING COMPARATORS and TREATMENTS

The clinical management of heart failure aims to relieve symptoms, reduce mortality and improve quality of life. The current treatment options for chronic heart failure due to left ventricular systolic dysfunction include\textsuperscript{1,11,14,23}:

• Lifestyle interventions, e.g. exercise training, smoking cessation support, low-salt diet.
• Pharmacological treatment:
  First line
  o Angiotensin-converting enzyme (ACE) inhibitors (e.g. enalapril, ramipril).
  o Angiotensin-II receptor blockers (ARBs) (e.g. candesartan cilexetil) as an alternative to an ACE inhibitor for patients who have intolerable side effects with ACE inhibitors.
  o Beta-blockers (e.g. bisoprolol and carvediol) should be administered to all patients with heart failure due to left ventricular systolic dysfunction.
  Second line
  o Aldosterone antagonist (spironolactone) for patients with moderate to severe HF (NYHA class II-IV\textsuperscript{b}) or MI in past month).
  o Hydralazine in combination with nitrate – patients who are intolerant of ACE inhibitors and ARBs.
  o Ivabradine in patients with a LVEF of 35% or less; in patients in sinus rhythm and whose heart rate is $\geq 75$ bpm, in combination with standard therapy including beta-blocker therapy, ACE inhibitors and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated.
  o Cardiac glycosides (digoxin) can be used if a patient in sinus rhythm remains symptomatic despite therapy with a diuretic, ACE inhibitor (or ARB) and beta-blocker or as first-line therapy in patients with atrial fibrillation.
  o Diuretics (e.g. thiazide diuretic, bendroflumethiazide, or a loop diuretic such as furosemide).
• Cardiac resynchronisation therapy – with a pacing device (CRT-P) may be considered for patients with all of the following:
  o sinus rhythm either with a QRS duration of 150ms or longer estimated by standard electrocardiogram (ECG) or with a QRS duration of 120-149ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography.

\textsuperscript{b} Expert clinical opinion.
o LVEF of 35% or less.

o receiving optimal pharmacological therapy.

**EFFFICACY and SAFETY**

<table>
<thead>
<tr>
<th><strong>Trial</strong></th>
<th>PARADIGM-HF, NCT01035255: LCZ696 vs enalapril; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sponsor</strong></td>
<td>Novartis pharmaceuticals.</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Ongoing.</td>
</tr>
<tr>
<td><strong>Source of information</strong></td>
<td>Trial registry,24 manufacturer.</td>
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<tr>
<td><strong>Location</strong></td>
<td>EU (incl UK), USA, Canada and other countries.</td>
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<tr>
<td><strong>Design</strong></td>
<td>Randomised, active-controlled.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>n=7,980 (planned); aged ≥18 years; chronic heart failure NYHA class II-IV; reduced LVEF (≤35%); elevated B-type natriuretic peptide; receiving ACE inhibitor OR ARB at a stable dose of at least enalapril 10mg once daily or equivalent for ≥4 weeks; on stable dose β-blocker, unless contraindicated for ≥4 weeks; not requiring treatment with both ACE Inhibitors and ARBs; no current acute decompensated heart failure.</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>Randomised to LCZ696 200mg oral twice daily, or enalapril 10mg oral twice daily.</td>
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<tr>
<td><strong>Follow-up</strong></td>
<td>Active treatment to first occurrence of the composite endpoint (defined as either cardiovascular (CV) death or heart failure hospitalisation).</td>
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<tr>
<td><strong>Primary outcome/s</strong></td>
<td>Time to first occurrence of the composite endpoint (defined as either CV death or heart failure hospitalisation) up to 4 years.</td>
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<td><strong>Secondary outcome/s</strong></td>
<td>KCCQ score up to 4 years; time to all-cause mortality up to 4 years; time to occurrence of renal dysfunction up to 4 years.</td>
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<tr>
<td><strong>Expected reporting date</strong></td>
<td>Estimated study completion date April 2014.</td>
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</tbody>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of LCZ696 is not yet known. The cost of a 28-tab pack of enalapril maleate 10mg is 95 pence. The cost of a 28-tab pack of the angiotensin II receptor blocker candesartan cilexetil 32mg is £16.13.25

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

☑ Reduced mortality/increased length of survival  ☐ Reduced symptoms or disability

☑ Other: *Company claim LCZ696 has the potential to improve safety by avoiding side effects associated with inhibition of the major bradykinin-degrading pathway.*

☐ No impact identified

☐ Other:

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*The Kansas City Cardiomyopathy Questionnaire (KCCQ): a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life.*
Impact on Services

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other: None identified

Impact on Costs

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- Other: uncertain unit cost compared to existing treatments
- None identified

Other Issues

- Clinical uncertainty or other research question identified:
- None identified

REFERENCES

17 McMurray JJV, Adamopoulos S, Anker DS et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Heart Journal 2012;33;1787-1847.
24 Clinicaltrials.gov. This study will evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality of patients with chronic heart failure (PARADIGM-HF). http://clinicaltrials.gov/ct2/show/NCT01035255?term=LCZ696+AND+heart+failure&rank=3 Accessed 05 June 2013.