Irbesartan (Aprovel) for heart failure with preserved systolic function

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Irbesartan (Aprovel) for heart failure with preserved systolic function

**Target group**
- Heart failure with preserved systolic function (HF-PSF) – symptomatic heart failure and a left ventricular ejection fraction (LVEF) of ≥ 45%.

**Technology description**
Irbesartan (Aprovel) is an oral angiotensin II receptor blocker (ARB) mainly used for treatment of hypertension. Its mode of action is to block the activation of angiotensin II AT₁ receptors which directly causes vasodilation, a reduction in the secretion of vasopressin and a reduction in the production and secretion of aldosterone, the combined effect of which is a reduction in blood pressure.

Irbesartan 150-300mg is given once daily. Irbesartan is currently licensed for the treatment of hypertension and renal disease in hypertensive type 2 diabetes mellitus.

Irbesartan is in phase III clinical trials for prevention of cardiovascular complications in patients with persistent atrial fibrillation.

**Innovation and/or advantages**
Irbesartan would be the first ARB licensed for patients with HF-PSF, and may increase survival and reduce the need for hospitalisation.

**Developer**
Bristol-Myers Squibb and sanofi-aventis.

**Availability, launch or marketing dates, and licensing plans:**
In phase III clinical trials.

**NHS or Government priority area:**
This topic is relevant to:

**Relevant guidance**
- NICE technology appraisal in development. Nesiritide for acute decompensated heart failure. Publication date to be confirmed¹.
- NICE technology appraisal. Cardiac resynchronisation therapy for the treatment of heart failure².
- SIGN. Management of chronic heart failure. 2007⁴.
- American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC). Guideline update for the diagnosis and management of chronic heart failure in the adult. 2005⁵.
Clinical need and burden of disease

Heart failure (HF) is a complex syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the heart to function as a pump to support a physiological circulation. The syndrome of HF is characterised by symptoms such as breathlessness and fatigue, and signs such as fluid retention¹.

The number of patients on Quality Outcomes Framework (QOF) disease registers with heart failure was 419,856 in the period 2006-2007, an unadjusted prevalence of 0.8% of all patients registered with a general practitioner in England⁶. The quality of life experienced by people with heart failure is generally worse than that for people with other chronic conditions, such as arthritis or chronic lung disease⁷. Prognosis is poor with almost 40% of those diagnosed dying within a year. There were 8,109 registered deaths from heart failure in England and Wales in 2006, 97% of these being in the 65 and over age group⁸. In 2005-2006 there were 63,306 admissions to hospital with a primary diagnosis of heart failure and 106,500 finished consultant episodes (ICD I50)⁹.

Over the past decade HF-PSF has become a clinical entity in its own right. Cohort studies of hospitalised patients suggest that a third to a half of patients thought to have clinical HF have preserved systolic function. Various studies have now reported that patients with this type of HF have a mortality rate which is lower than HF with reduced systolic function (HF-RSF) but is still high overall¹⁰.

Existing comparators and treatments

Optimal management of HF-PSF is not yet established⁶. NICE recommended that patients with diastolic dysfunction are treated with a low to medium dose of loop diuretics¹. Patients not responding to this treatment would require further specialist advice.

Other therapies for systolic heart failure include:

- Angiotensin-converting enzyme (ACE) inhibitors (e.g. ramipril).
- Angiotensin-II receptor antagonists (e.g. candesartan cilexetil) can be a useful alternative for patients who cannot tolerate ACE inhibitors (currently licensed for heart failure with reduced left ventricular function).
- Beta-blockers (e.g. bisoprolol and carvediol).
- Aldosterone antagonist (spironolactone) for patients with moderate to severe HF who are already receiving an ACE inhibitor and a beta-blocker.
- Diuretics (e.g. thiazide diuretic, bendroflumethiazide, or a loop diuretic such as furosemide).
- Digoxin can be used if a patient in sinus rhythm remains symptomatic despite therapy with a diuretic, ACE inhibitor (or angiotensin II receptor antagonist) and beta-blocker or as first-line therapy in patients with atrial fibrillation.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial code</th>
<th>NCT00095238¹¹, I-Preserve: irbesartan vs placebo; phase III</th>
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<tr>
<td>Sponsor</td>
<td>sanofi-aventis</td>
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<td>Status</td>
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<tr>
<td>Location</td>
<td>North America, South America, Australia, Europe</td>
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<tr>
<td>Design</td>
<td>Randomised, double blind, placebo control</td>
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</table>

¹¹ British National Formulary No. 55, March 2008
Participants in trial  
- n= 4,500; age ≥ 60 years with HF-PSF, LVEF ≥ 45%; hospitalisation for HF within the past 6 months or pre-specified abnormalities in electrocardiogram (ECG), or echocardiogram or chest x-ray indicating heart disease. Randomised to irbesartan 300mg daily or placebo.

Follow-up  
- 6 years

Primary outcome  
- Time from randomisation to the first occurrence of the composite outcome of death (all cause) or cardiovascular hospitalisation.

Secondary outcomes  
- Cardiovascular death, all cause mortality, combined vascular endpoint: cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke.

Expected reporting date  
- -

Estimated cost and cost impact  
- The annual cost of irbesartan 300mg once daily is £220b.

Potential or intended impact – speculative

Patients  
- ☑ Reduced morbidity  
- ☑ Reduced mortality or increased survival  
- ☑ Improved quality of life for patients and/or carers  
- ☐ Other:  
- ☐ None identified

Services  
- ☐ Increased use  
- ☐ Service reorganisation required  
- ☐ Staff or training required  
- ☑ Decreased use: e.g. fewer and shorter hospital stays  
- ☐ Other:  
- ☐ None identified

Costs  
- ☐ Increased unit cost compared to alternative  
- ☑ New costs: new drug class for patients with HF-PSF  
- ☑ Increased costs: more patients coming for treatment  
- ☑ Increased costs: capital investment needed  
- ☐ Savings: fewer and shorter hospital stays  
- ☐ Other:

References

5 American College of Cardiology/American Heart Association/European Society of Cardiology guidelines. Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult. 2005.
6 The Information Centre for Health and Social care - Prescribing Support Unit, QMAS database – 2006/7 as at end of June 2007.

b British National Formulary No. 55, March 2008
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