Serelaxin for acute decompensated heart failure – in addition to IV diuretics

SUMMARY **NIHR HSC ID: 788**

Serelaxin is intended to be administered in addition to IV diuretic treatment in patients hospitalised with acute heart failure (AHF), with normal to elevated blood pressure and mild to moderate renal impairment. If licensed, serelaxin could offer an alternative treatment option for this patient group. Currently used IV vasodilators are associated with known restrictions such as intolerance, contraindications or uncertainty about long-term safety. Serelaxin is a synthetic analogue of a naturally occurring peptide hormone with cardio-renal function-enhancing properties.

Heart failure is a common condition; more than 392,853 patients registered with general practitioners in England were diagnosed with this condition in 2010-2011, an unadjusted prevalence of 0.7% of all patients registered. In England, there were 60,000 admissions for heart failure (ICD10 I50) in 2010-11, approximately half of which were for AHF, resulting in 117,034 finished consultant episodes and 739,668 bed days.

Treatment for AHF aims to improve symptoms (dyspnoea and/or fatigue), stabilise the patients' haemodynamic condition, prevent recurrence and improve survival. Treatment options include oxygen and ventilator assistance; morphine for severe dyspnoea, agitation or pain; diuretics and loop diuretics; vasodilators; and inotropic agents. Serelaxin in addition to IV diurectics is currently in a phase III clinical trial comparing its effect on dyspnoea (primary outcome) against treatment with IV diurectics alone. This trial is expected to complete in September 2012.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

NIHR Horizon Scanning Centre, University of Birmingham
Email: nihrhsc@contacts.bham.ac.uk
Web: www.nhsc-healthhorizons.org.uk

NHS National Institute for Health Research

TARGET GROUP

- Acute decompensated heart failure (AHF) – in addition to IV diuretics.

TECHNOLOGY

DESCRIPTION

Serelaxin (Recombinant relaxin; RLX030) is a synthetic analogue of a naturally occurring peptide hormone with cardio-renal function-enhancing properties. Endogenous relaxin modulates cardiovascular responses to pregnancy, including increased vasodilation, decreased systemic vascular resistance, increased cardiac output and global arterial compliance, and increased renal function[1]. Evidence from clinical and nonclinical studies suggests that endogenous relaxin can also effect cardiovascular changes in the non-pregnant state when exogenously administered.

Serelaxin is intended to be administered in addition to IV diuretic treatment in patients hospitalised with AHF with normal to elevated blood pressure and mild to moderate renal impairment. In the clinical trial, it is administered by 48 hour IV infusion at 30µg/kg daily.

INNOVATION and/or ADVANTAGES

If licensed, serelaxin could offer an alternative treatment option for this patient group. Currently used IV vasodilators are associated with known restrictions such as intolerance, contraindications or uncertainty about long-term safety[1,2,3].

DEVELOPER

Novartis General Medicines.

PATIENT GROUP

BACKGROUND

Acute decompensated heart failure represents a heterogeneous group of disorders that typically present as dyspnoea, edema and fatigue[4]. The term acute decompensated heart failure broadly represents new or worsening symptoms or signs of dyspnoea, fatigue or edema that lead to hospital admission or unscheduled medical care and that are consistent with an underlying worsening of left ventricular function[4]. Acute heart failure defined as the onset of symptoms or signs of heart failure in a patient with no prior history of heart failure and previously normal function is an uncommon cause of acute decompensated heart failure, particularly in patients without concomitant acute coronary syndromes. Much more frequently, acute decompensated heart failure occurs in patients with previously established myocardial dysfunction (systolic or diastolic) who present with an exacerbation of symptoms or signs after a period of relative stability[4].

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

- The National Service Framework for Coronary Heart Disease (2005).
- The National Service Framework for Older People (2001).

CLINICAL NEED and BURDEN OF DISEASE

Heart failure is a common condition; more than 392,853 patients registered with general practitioners in England were diagnosed with this condition in 2010-2011, an unadjusted prevalence of 0.7% of all patients registered[5]. Heart failure tends to affect older people, with a median age at diagnosis of 76 years, and there is a significantly higher incidence in men[6,7]. AHF accounts for approximately 5% of emergency medical admissions in the UK, and most of the costs of managing heart failure relate to the cost of these admissions[a]. In England, there were 60,000 admissions for heart failure (ICD10 I50) in 2010-11, approximately half of which were for AHF[a], resulting in 117,034 finished consultant episodes and 739,668 bed days[8]. Registries indicate that almost half of those hospitalised with AHF are re-hospitalised at least once within 12 months[3]. In 2005-2006, around 83% of patients received diuretics on admission for heart failure in England, Wales and Northern Ireland[6].

The quality of life of patients hospitalised with AHF is low, with 47% or more exhibiting self-care problems, walking disorders, difficulties performing usual activities, pain or discomfort, anxiety or depression[6]. Prognosis is poor, with approximately 40% of patients dying within a year[6]. In 2010, heart failure (ICD10 I50) accounted for 8,135 deaths in England, though death figures are widely acknowledged to be underestimated[6,9].

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Ivabradine for the treatment of chronic heart failure. Expected December 2012[10].
- NICE technology appraisal. Cardiac resynchronisation therapy for the treatment of heart failure. 2007[11].
- NICE clinical guideline in development. Diagnosis and management of acute heart failure[12]. Expected date of issue to be confirmed.
- NICE clinical guideline. Management of chronic heart failure in adults in primary and secondary care. 2010[13].

Other Guidance

- The European Society of Cardiology. Guidelines for the diagnosis and treatment of acute and chronic heart failure. 2008[3].
- SIGN. Management of chronic heart failure. 2007[14].

[a] Expert communication.

EXISTING COMPARATORS and TREATMENTS

Treatment for AHF aims to improve symptoms (dyspnoea and/or fatigue), stabilise the patients' haemodynamic condition, prevent recurrence and improve survival[3,b]. Options include:

- Oxygen and ventilator assistance.
- Morphine for severe dyspnoea, agitation or pain.
- Diuretics and loop diuretics e.g. furosemide, bumetandine, torasemide, thiazides.
- Vasodilators e.g. nitrates, sodium nitroprusside, neseritide (unlicensed).
- Inotropic agents e.g. dopamine, dobutamine, levosimendan.

EFFICACY and SAFETY

Trial	RELAX-AHF, NCT00520806, RLX.CHF.003; RLX030 (serelaxin) vs placebo, both with furosemide (or alternative loop diuretic); phase III.
Sponsor	Corthera Inc (a Novartis company).
Status	Ongoing.
Source of information	Publication[1], trial registry[15], manufacturer.
Location	EU (inc UK),USA and other countries.
Design	Randomised, placebo-controlled.
Participants	n=1,160 (planned); adults; AHF; systolic blood pressure >125mmHg; impaired renal function[c]; receiving ≥40 mg of intravenous furosemide (or equivalent dose of alternative loop diuretic) within 16 hrs of presentation.
Schedule	Randomised to RLX030 at 30µg/kg daily or placebo, both adminstered by 48 hour IV infusion.
Follow-up	Active treatment period 48 hrs; short-term follow-up through to day 5 and at day 14, and intermediate term follow-up at 60 and 180 days.
Primary outcome/s	Relief of dyspnoea: markedly/moderately better dyspnoea on visual analogue scale (VAS) through day 5, and on the 7-point Likert scale at 6, 12 and 24 hrs.
Secondary outcome/s	Days alive out of hospital through day 30 or 60; composite endpoint of cardiovascular death/rehospitalisation with heart failure/renal failure through day 60; dyspnoea (VAS and 7-point Likert scale) through day 14; time to worsening heart failure up to day 5 and day 14; total doses IV loop/oral diuretics through day 5 (or discharge if earlier); weight change through day 5 and 14; length of hospital stay; all-cause death, worsening heart failure, rehospitalisation for heart failure, and renal failure through day 60; cardiovascular death through day 180; subject and investigator reported signs/symptoms of heart failure; ICU/CCU days.
Key results	Pre-RELAX-AHF (Phase IIb) results: For RLX030 30µg/kg daily (n=42) vs placebo (n=61) respectively: improved dyspnoea assessed by Likert scale at 6, 12 and 24 hrs, 40% vs 23% (p=0.44); improved dyspnoea assessed by VAS through day 14, 8,214 vs 4,622mm x hour (p=0.053); length of hospital stay, 10.2 vs 12.0 days (p=0.18); days alive out of hospital, 47.9 vs 44.2 (p=0.16); cardiovascular death/rehospitalisation due to heart failure or renal failure, 2.6% vs 17.2% (p=0.053).
Adverse effects (AEs)	Pre-RELAX-AHF (Phase IIb): serious AEs were reportedly similar between groups.
Expected reporting date	Sept 2012.

[b] Expert communication.

[c] Defined as an estimated glomerular filtration rate of 30-75 mL/min/1.73m^2.

ESTIMATED COST and IMPACT

COST

The cost of serelaxin is not yet known. The costs of selected IV vasodilators (nitrates and neseritide) are as follows:

Drug	Dose[3]	Unit cost[16]
Nitroglycerine (glyceryl trinitrate)	Start 10–20µg/min, increase up to 200µg/min.	£15.90 for 50ml vial (1mg/ml).
Isosorbide dinitrate (Isoket)	Start with 1mg/hour, increase up to 10mg/hour.	£2.69 for 10ml amp (1mg/ml).
Nitroprusside	Start with 0.3µg/kg/min and increase up to 5µg/kg/min.	No price (available as special order from manufacturer).
Nesiritide (Noratak)	Bolus 2µg/kg infusion 0.015–0.03µg/kg/min.	Unlicensed in the UK.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- ☑ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☐ Other
- ☐ No impact identified

Impact on Services

- ☑ Increased use of existing services: 48 hour IV infusion
- ☑ Decreased use of existing services: Potential for improved symptom control (dyspnoea and general well being)
- ☐ 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: new costs
- ☐ None identified

Other Issues

- ☐ Clinical uncertainty or other research question identified
- ☑ None identified

REFERENCES

[1] Teerlink JR, Metra M, Felker GM *et al*. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose finding phase IIb study. The Lancet 2009;373,9673:1429-1439.
[2] Map of Medicine. Heart failure (HF): acute or decompensated.

http://app.mapofmedicine.com/mom/1/page.html?department-id=4&specialty-id=1018&pathway-id=11278&page-id=11385&pathway-prov-cert=/attachments/14970_provcert.pdf&history=clear Accessed 14 July 2011

[3] The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology, ESC Guidelines on the diagnosis and treatment of acute and chronic heart failure. European Heart Journal 2008;29:2388-2442.

[4] Allen LA and O'Connor CM. Management of acute decompensated heart failure. Canadian Medical Association 2007;176(6):797-805.

[5] The Information Centre for Health and Social care - Prescribing Support Unit, QMAS database – 2010/11 http://www.ic.nhs.uk/statistics-and-data-collections/supporting-information/audits-and-performance/the-quality-and-outcomes-framework/qof-2010-11/qof-2010-11-data-tables/qof-prevalence-data-tables-2010-11 Accessed 23 May 2012.

[6] Sutherland K. Evidence. The Health Foundation. Bridging the quality gap: heart failure. March 2010 http://www.health.org.uk/public/cms/75/76/313/583/Bridging%20the%20quality%20gap%20Heart%20Failure.pdf?realName=cXqFcz.pdf Accessed 23 May 2012.

[7] NHS Choices. Heart failure. http://www.nhs.uk/Conditions/Heart-failure/Pages/Introduction.aspx Accessed 23 May 2012.

[8] NHS. Hospital Episodes Statistics, Inpatient data 2010-2011, Primary diagnosis: 3 character table. http://www.hesonline.nhs.uk Accessed 23 May 2012.

[9] Office for National Statistics. Mortality statistics: Deaths registered in 2010 (Series DR). http://www.ons.gov.uk Accessed 23 May 2012.

[10] National Institute for Health and Clinical Excellence. Ivabradine for the treatment of chronic heart failure. Technology appraisal in development ID484. Expected December 2012.

[11] National Institute for Health and Clinical Excellence. Cardiac resynchronisation therapy for the treatment of heart failure. Technology appraisal TA120. London: NICE; May 2007.

[12] National Institute for Health and Clinical Excellence. Diagnosis and management of acute heart failure. Clinical guideline in development. Publication date not yet confirmed.

[13] National Institute for Health and Clinical Excellence. Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. Clinical guideline CG108. London: NICE; August 2010.

[14] Scottish Intercollegiate Guideline Network. Management of chronic heart failure: A national clinical guideline, No. 95. SIGN: Edinburgh; February 2007.

[15] ClinicalTrials.gov. Efficacy and safety of relaxin for the treatment of acute heart failure (RELAX-AHF) http://clinicaltrials.gov/ct2/show/study/NCT00520806 Accessed 23 May 2012.

[16] British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. BNF 63. London: BMJ Group and RPS Publishing, March 2012.