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

### SUMMARY

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 diuretics is currently in a phase III clinical trial comparing its effect on dyspnoea (primary outcome) against treatment with IV diuretics alone. This trial is expected to complete in September 2012.
### 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\(^4\).
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\(^8\). In England, there were 60,000 admissions for heart failure (ICD10 I50) in 2010-11, approximately half of which were for AHF\(^8\), 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\(^6,9\).
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.\(^b\) 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

<table>
<thead>
<tr>
<th>Trial</th>
<th>RELAX-AHF, NCT00520806, RLX.CHF.003; RLX030 (serelaxin) vs placebo, both with furosemide (or alternative loop diuretic); phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Corthera Inc (a Novartis company).</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Publication(^1), trial registry(^1), manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (inc UK), USA and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=1,160 (planned); adults; AHF; systolic blood pressure &gt;125mmHg; impaired renal function(^c); receiving ≥40 mg of intravenous furosemide (or equivalent dose of alternative loop diuretic) within 16 hrs of presentation.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to RLX030 at 30µg/kg daily or placebo, both administered by 48 hour IV infusion.</td>
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<td>Follow-up</td>
<td>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.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>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.</td>
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<tr>
<td>Secondary outcome/s</td>
<td>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.</td>
</tr>
<tr>
<td>Key results</td>
<td>Pre-RELAX-AHF (Phase Ib) 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).</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>Pre-RELAX-AHF (Phase Ib): serious AEs were reportedly similar between groups.</td>
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<td>Expected reporting date</td>
<td>Sept 2012.</td>
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</tbody>
</table>

\(^b\) 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:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose*</th>
<th>Unit cost†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerine</td>
<td>Start 10–20µg/min, increase up to 200µg/min.</td>
<td>£15.90 for 50ml vial (1mg/ml).</td>
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<tr>
<td>(glyceryl trinitrate)</td>
<td></td>
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<tr>
<td>Isosorbide dinitrate</td>
<td>Start with 1mg/hour, increase up to 10mg/hour.</td>
<td>£2.69 for 10ml amp (1mg/ml).</td>
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<tr>
<td>(Isoket)</td>
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<tr>
<td>Nitroprusside</td>
<td>Start with 0.3µg/kg/min and increase up to 5µg/kg/min.</td>
<td>No price (available as special order from manufacturer).</td>
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<tr>
<td>Neseritide (Noratak)</td>
<td>Bolus 2µg/kg infusion 0.015–0.03µg/kg/min.</td>
<td>Unlicensed in the UK.</td>
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### 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