Ularitide for acute decompensated heart failure – first line

SUMMARY

Ularitide is intended to be used as first line therapy for the treatment of acute decompensated heart failure (ADHF). If licensed, it would offer an alternative treatment option for this patient group. Ularitide is the chemically synthesised form of urodilatin, a naturally occurring peptide hormone. Urodilatin induces natriuresis and diuresis by binding to the natriuretic peptide receptor in the cortical and inner medullary collecting duct of the kidney, thereby increasing intracellular levels of cyclic guanosine monophosphate (cGMP). It is not licensed for any other indication.

Heart failure (HF) is a common condition; more than 395,240 patients registered with general practitioners in England were diagnosed with this condition in 2011-2012, an unadjusted prevalence of 0.7% of all patients registered. In England, there were 61,130 admissions for HF in 2011-12, resulting in 121,242 finished consultant episodes and 741,973 bed days. In 2010, heart failure accounted for 5,378 deaths in England, though this is widely acknowledged to be an underestimate.

Treatment for ADHF aims to improve symptoms, stabilise the patient’s haemodynamic condition, prevent recurrence and improve survival. Options include oxygen and ventilator assistance, diuretics and vasodilators. Ularitide is currently in one phase III clinical trial comparing its effect on change in symptoms and persistent or worsening heart failure requiring a further intervention within 48 hours against treatment with placebo. This trial is expected to complete in September 2014.
TARGET GROUP

- Acute decompensated heart failure – first line.

TECHNOLOGY

DESCRIPTION

Ularitide (ANF 95-126; ANP 95126; urodilatin) is the chemically synthesised form of urodilatin, a naturally occurring peptide hormone. Urodilatin induces natriuresis and diuresis by binding to the natriuretic peptide receptor in the cortical and inner medullary collecting duct of the kidney, thereby increasing intracellular levels of cyclic guanosine monophosphate (cGMP). It is intended as the first line treatment of acute decompensated heart failure. Ularitide is administered as a 48 hour intravenous (IV) infusion at 15ng/kg/min.

INNOVATION and/or ADVANTAGES

If licensed, ularitide could offer an alternative treatment option for this patient group.

DEVELOPER

Cardiorentis Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Acute decompensated heart failure (ADHF) can be defined as the sudden or gradual onset of the signs and symptoms of heart failure requiring unplanned visits to primary care, A&E departments, and in-patient hospital admissions. It represents a heterogeneous group of disorders that typically present as dyspnoea, peripheral and pulmonary oedema, and fatigue. Acute heart failure (AHF) 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 ADHF, particularly in patients without concomitant acute coronary syndromes. More often, ADHF occurs in patients with previously established myocardial dysfunction (systolic or diastolic) and heart failure, who present with an exacerbation of symptoms or signs after a period of relative stability. Acute coronary syndromes, atrial tachy-arrhythmias, infection, anaemia and renal dysfunction are common factors precipitating or exacerbating ADHF.

\[a\] Expert personal communication.
This topic is relevant to:

Heart failure (HF) is a common condition; more than 395,240 patients registered with general practitioners in England were diagnosed with this condition in 2011-2012, an unadjusted prevalence of 0.7% of all patients registered. However, expert opinion suggests that about 2% of patients in primary care take loop diuretics and it is likely that many of these are undiagnosed HF patients. HF tends to affect older people, with a median age at diagnosis of 76 years, and the incidence in men and women is similar. ADHF is the primary reason for about 1% of emergency admissions in the UK, but may also contribute to a further 4%. Most of the costs of managing heart failure relate to the cost of these admissions. In England, there were 61,130 admissions for heart failure (ICD-10 I50) in 2011-12, resulting in 121,242 finished consultant episodes and 741,973 bed days. Registries indicate that almost half of those hospitalised with AHF are re-hospitalised at least once within 12 months.

The quality of life of patients hospitalised with ADHF is low, with 47% or more exhibiting self-care problems, walking disorders, difficulties performing usual activities, pain or discomfort, anxiety or depression. Prognosis is poor, with approximately 40% of patients dying within a year. In 2010, heart failure (ICD-10 I50) accounted for 5,378 deaths in England, though this is widely acknowledged to be an underestimate.

Relevant Guidance

**NICE Guidance**
- NICE clinical guideline in development. Diagnosis and management of acute heart failure. Expected date of issue September 2014.

**Other Guidance**
EXISTING COMPARATORS and TREATMENTS

Treatment for ADHF aims to improve symptoms (dyspnoea and/or fatigue), stabilise the patient’s haemodynamic condition, prevent recurrence and improve survival\(^8\,\text{c}\). Options include:

- Oxygen and ventilator assistance (including use of continuous positive airway pressure, CPAP).
- Morphine for severe dyspnoea, agitation or pain.
- Diuretics e.g. furosemide, bumetanide, torasemide (loop diuretics), or thiazides in conjunction with loop diuretics.
- Vasodilators e.g. nitrates, sodium nitroprusside, neseritide (unlicensed).
- Inotropic agents e.g. dopamine, dobutamine.
- ACE inhibitors, angiotensin receptor blockers and/or aldosterone antagonists – typically administered soon after admission\(^9\).

Efficacy and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01661634, ULA01, 2010-024249-59; ularitide vs placebo; phase III.</th>
<th>SIRIUS II; ularitide vs placebo; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Cardiorentis Ltd.</td>
<td>Cardiopep GmbH.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^15).</td>
<td>Publication(^16,\text{c},\text{d}).</td>
</tr>
<tr>
<td>Location</td>
<td>EU, USA, Canada and other countries.</td>
<td>German, Russia and Serbia.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n= 2,116 (planned); 18-85 years; ADHF; systolic blood pressure &gt;100mgHg.</td>
<td>n=221; 8-85 years; ADHF.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to ularitide 15ng/kg/min or placebo, both as a 48 hour continuous IV infusion.</td>
<td>Randomised to ularitide 7.5ng/kg/min, 15ng/kg/min, 30ng/kg/min, or placebo, all as a 24 hour continuous IV infusion.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment period 48 hours, follow-up 180 days.</td>
<td>Active treatment period 24 hours, follow-up 30 days.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Change in symptoms; persistent or worsening heart failure requiring an intervention up to 48 hours; all-cause mortality; cardiovascular rehospitalisation at 30 days; safety.</td>
<td>Change in pulmonary capillary wedge pressure (PCWP) at 6 hours; change in patient’s self-assessed dyspnoea score at 6 hours.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Changes of N-terminal pro brain natriuretic peptide (NT-pro BNP); all-cause mortality and cardiovascular rehospitalisation; cardiovascular mortality.</td>
<td>Right atrial pressure (RAP); cardiac output; systolic blood pressure (SBP); heart rate (HR); electrocardiographic status; safety.</td>
</tr>
<tr>
<td>Key results</td>
<td>-</td>
<td>For ularitide 7.5ng/kg/min, 15ng/kg/min, 30ng/kg/min, and placebo respectively (p value vs placebo): PCWP at 6 hours, -6.2mmHg, -10.9mmHg (p=0.005), -9.5mmHd (p=0.003) vs -4.5mmHg; RAP at 8 hours, 7.2mmHg, 6.8mmHg, 7.2mmHg vs 8.5mmHg; SBP at 6 hours, -7mmHg, -11mmHg, -15mmHg vs -5mmHg; HR change from baseline, -2.8 to 1.5 beats per min (b.p.m), -1.4 to 2.6 b.p.m, -2.2 to 1.8 b.p.m vs -1.0 to 2.0</td>
</tr>
</tbody>
</table>

\(^c\) Expert personal communication.
b.p.m; dyspnoea score at 6 hours, 38% (p=0.0026), 45% (p=0.0026), 48% (p=0.0013) vs 25%.

Adverse effects (AEs) - AEs include: BP decrease, 5.4%; hypotension, 5.4%; sweating, 4.2%; dizziness, 3.0%.

Expected reporting date Primary completion date reported as Sept 2014.

### ESTIMATED COST and IMPACT

#### COST

The cost of ularitide is not yet known. The cost of selected IV vasodilators (nitrates and neseritide) and inotropes are as follows[^8][^18].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerine (glyceryl trinitrate)</td>
<td>Start 10–20μg/min, increase up to 200μg/min.</td>
<td>£15.90 for 50ml vial (1mg/ml).</td>
</tr>
<tr>
<td>Isosorbide dinitrate (Isoket)</td>
<td>Start with 1mg/hour, increase up to 10mg/hour.</td>
<td>£2.69 for 10ml ampoule (1mg/ml).</td>
</tr>
<tr>
<td>Nesiritide (Noratak)</td>
<td>Bolus 2μg/kg infusion 0.015–0.03μg/kg/min.</td>
<td>Unlicensed in the UK.</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2.5-10mg/kg/minute, adjusted according to response.</td>
<td>£7.50 for 50ml vial (5mg/ml).</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2-5mg/kg/minute.</td>
<td>£3.40 for 5ml ampoule (160mg/ml).</td>
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</tbody>
</table>

#### IMPACT - SPECULATIVE

**Impact on Patients and Carers**
- Reduced mortality/increased length of survival
- Other: Reduced symptoms or disability
- No impact identified

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

**Impact on Costs**
- Increased drug treatment costs
- Other increase in costs: expert opinion states that there may be an increase in cost if there is a short-term increased length of survival.
- Other: uncertain unit cost compared to existing treatments.
- Reduced drug treatment costs
- Other reduction in costs: expert opinion states that there may be a reduction in cost due to reduced duration of hospitalisation.
- None identified

[^8]: Needs to be referenced.
[^18]: Needs to be referenced.
Other Issues

☑ Clinical uncertainty or other research question identified: expert opinion indicates that the exclusion of patients with a systolic BP of <110mmHg may improve safety and efficacy but excludes 10-20% of the sickest patients with ADHF.

☐ None identified

REFERENCES

8 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.