Oral calcitonin for osteoarthritis of the knee in men and postmenopausal women – first line

August 2010

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Oral calcitonin for osteoarthritis of the knee in men and postmenopausal women – first line

**Target group**
- Osteoarthritis (OA) of the knee in men and postmenopausal women – first line; monotherapy or in combination with symptom modifying OA drugs.

**Technology description**
Oral calcitonin (oral salmon calcitonin, salmon calcitonin, SMC-021) is an oral formulation of salmon calcitonin with 5-CNAC, a unimolecular enhancer of gastrointestinal absorption of the peptide hormone. Salmon calcitonin inhibits osteoclast activity, strengthens subchondral bone and has chondroprotective, chondroanabolic and musculoskeletal analgesic effects. It is intended both as a substitute and an addition to current symptom modifying drugs for the treatment of OA of the knee in men and postmenopausal women. Oral calcitonin is administered orally at 0.8mg twice daily.

Oral calcitonin is also in phase III clinical trials for the treatment of postmenopausal osteoporosis.

Salmon calcitonin is also available in an intranasal formulation to reduce the risk of vertebral fractures in postmenopausal osteoporosis, and in an intravenous formulation for the treatment of Paget’s disease, hypercalcaemia of malignancy and prevention of acute bone loss due to immobilisation.

**Innovation and/or advantages**
If licensed, oral calcitonin will be the first drug to possess both disease modifying and symptom relief activity for OA of the knee.

**Developer**
Novartis Pharmaceuticals.

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

**NHS or Government priority area**
This topic is relevant to The Musculoskeletal Services Framework (2006) and the National Service Framework for Older People (2001).

**Relevant guidance**
- NICE technology appraisal in development. Cox-II inhibitors for the treatment of osteoarthritis and rheumatoid arthritis. Expected date of issue to be confirmed¹.
- NICE clinical guideline. The care and management of osteoarthritis. 2008².

Clinical need and burden of disease
The prevalence of OA is difficult to determine because the clinical syndrome (joint pain and stiffness) does not always correspond with the structural changes of OA visible at X-ray. OA of the knee is thought to affect more than 6 million people in the UK, with prevalence increasing with age from 1 in 5 adults aged 50–59 years to 1 in every 2 adults aged over 80 years. It is more common in elderly women than elderly men. At least 0.5 million people in the UK have X-ray evidence of moderate to severe OA of the knee. With an increasingly ageing population and increase in risk factors like obesity and poor levels of physical fitness, the prevalence of OA of the knee in the UK is increasing.

OA of the knee is a leading cause of pain and disability in the UK. An estimated 22% of adults aged 45-64 years and 35% of women aged 75 years and over report knee pain attributable to OA. Osteoarthritic knee pain causes disability in about 25% of adults aged 50 and over.

In 2008-09 in England there were 107,716 finished consultant episodes with a primary diagnosis of OA of the knee (ICD M17) of which 57% (61,390) were in females. Over 90% of knee replacement operations are due to OA. In 2009, approximately 17 million prescriptions were dispensed for NSAIDs, at a cost of almost £96 million in England and Wales.

Existing comparators and treatments
Guidelines for OA care recommend a holistic approach, taking into account the global needs of an individual.

Current management options for OA of the knee include:
- Patient education and self management interventions (e.g. use of suitable footwear).
- Thermotherapy.
- Exercise and manual therapy.
- Weight loss for people who are obese or overweight.
- Electrotherapy (e.g. TENS).
- Aids and devices (e.g. braces, joint supports, insoles and walking sticks).
- Arthroscopic lavage and debridement - recommended for people with a clear history of mechanical locking.
- Pharmacological interventions for pain relief:
  - Acetaminophen (paracetamol).
  - Topical NSAID or capsaicin.
  - Oral NSAIDs (e.g. ibuprofen, naproxen) or selective COX-2 inhibitors (e.g. celecoxib).
  - Opioids (e.g. codeine).
  - Intra-articular injections [e.g. corticosteroid injections, hyaluronan injections (not recommended by NICE)].
- Joint replacement surgery – recommended for people whose quality of life is substantially impacted by joint symptoms and who are refractory to non-surgical treatment.

Efficacy and safety
<p>| Trial | NCT00486434; oral calcitonin or placebo; phase III. | NCT00704847; oral calcitonin or placebo; phase III. |</p>
<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Novartis Pharmaceuticals and Nordic Bioscience A/S.</th>
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<tr>
<td>Status</td>
<td>Ongoing</td>
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<td>Source of information</td>
<td>Trial registry(^{14}), manufacturer.</td>
<td>Trial registry(^{15}), manufacturer.</td>
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<td>Location</td>
<td>EU and Hong Kong.</td>
<td>EU (inc UK), USA, Canada and Hong Kong.</td>
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<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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| Participants and schedule       | n=1150 (planned); adults aged 51-80 years; women at least 2 years post menopause; the signal knee should:  
  - fulfil American College of Rheumatology (ACR) criteria for OA of knee.  
  - fulfil Kellegren and Lawrence index of grades II-III at medial tibio-femoral joint.  
  - fulfil American Rheumatism Association (ARA) criteria for classification of functional class I, II or III.  
  - have joint space width (JSW) of ≥2mm in medial tibio-femoral joint.  
  - have WOMAC\(^{a}\) pain sub scale scores of ≥150mm and/or WOMAC function subscale score of ≥510mm.  
  Randomised to oral calcitonin at 0.8mg twice daily or placebo. | n=820; adults aged 51-80 years; women at least 2 years post menopause; the signal knee should:  
  - fulfil ACR criteria for OA of knee.  
  - fulfil Kellegren and Lawrence index of grades II-III at medial tibio-femoral joint.  
  - fulfil ARA criteria for classification of functional class I, II or III.  
  - have JSW of ≥2 mm in medial tibio-femoral joint.  
  - have WOMAC pain sub scale score of ≥150mm and/or WOMAC function subscale score of ≥510mm.  
  Randomised to oral calcitonin at 0.8mg twice daily or placebo. |
| Follow-up                       | Active treatment period 24 months, then 4 weeks follow up. | Active treatment period 24 months, then 4 weeks follow up. |
| Primary outcomes                | JSW in the medial tibio-femoral joint; pain and functional disability assessed by WOMAC pain and functional sub scale. | JSW in the medial tibio-femoral joint. |
| Secondary outcomes              | Composite of WOMAC scores; pain, physical activity and global assessment by Visual Analogue Scale (VAS); disease progression; effect on hand OA; biochemical markers of bone and cartilage metabolism; safety. | WOMAC functional and stiffness sub scale scores; composite of WOMAC scores; pain, physical activity and global assessment by VAS; quality of life by EQ-5D; disease progression; biochemical markers of bone and cartilage metabolism; safety. |
| Expected reporting date         | Study expected to report Q3 2010.                   | Study expected to complete August 2011.             |

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\(^{a}\)Western Ontario and McMaster Universities Osteoarthritis Index.
Participants and schedule

| n=53; adults aged 55-80 years; OA of medial tibio-femoral compartment of knee; enhanced and extended uptake of bone-seeking agent on bone scan; score III on Kellgren and Lawrence scale; LAFI\(^b\) score >7; morning joint stiffness < 30 minutes; pain on weight bearing and motion; prior treatment with antirheumatic drug; treatment with paracetamol 2-3g per day for 15 days until randomisation. Randomised to oral calcitonin (OC) once daily at 0.5mg or 1mg, or placebo. |

Follow-up

| Active treatment period 84 days. |

Primary outcomes

| Pain and functional disability assessed by LAFI; biomarkers of joint metabolism. |

Key results

| On day 42 and 84 groups receiving placebo and 1mg OC showed statistically significant (p<0.01) but similar decrease in median pain scores; 0.5mg OC group showed statistically significant (p<0.05) decrease in median pain scores on day 84. |
| On days 42 and 84 a significant (p<0.01) reduction in the function scores was observed in the two OC groups but not placebo; no statistically significant difference between the three groups was observed for median function scores at baseline, day 42 and 84. |
| On day 84, significant (p<0.05) reductions in levels of MMP-13 and hyaluronan observed in the two OC groups; group receiving 1mg OC showed significant (p<0.05) decrease in levels of CTX-II, C2C and MMP-13 biomarkers. |

Adverse effects

| Not reported. |

Estimated cost and cost impact

The cost of oral calcitonin is not yet known.

Claimed or potential impact – speculative

Patients

- Reduced mortality or increased length of survival
- Reduction in associated morbidity or improved quality of life for patients and/or carers
- Quicker, earlier or more accurate diagnosis or identification of disease
- None identified

Services

- Increased use
- Decreased use
- Service organisation
- Other: None identified

Costs

- Increased unit cost compared to alternative
- New costs:

- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed
- Savings:
- Other:

References


\(^b\) Lequesne’s Algfunctional Index.

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The National Horizon Scanning Centre,
Department of Public Health and Epidemiology
University of Birmingham, 90 Vincent Drive, Edgbaston, Birmingham, B15 2SP, England
Tel: +44 (0)121 414 7831 Fax +44 (0)121 414 2269
www.haps.bham.ac.uk/publichealth/horizon