Odanacatib for male osteoporosis – first and second line

SUMMARY

Odanacatib is intended to be used as therapy for the treatment of men with osteoporosis following bisphosphonate therapy in patients who cannot tolerate, do not wish to persist with or do not respond to oral bisphosphonates, or first-line in patients who are contraindicated for oral bisphosphonate therapy. Odanacatib is a cathepsin K inhibitor and if licensed, will offer an additional oral treatment option for males with osteoporosis.

Osteoporosis is a common condition that affects 1 in 3 women and 1 in 5 men over the age of 50, with a lifetime risk of fracture in this age group being estimated at 50% in women and 20-30% in men. Around 50% of men with osteoporosis have at least one secondary cause, which most commonly include treatment with glucocorticoids, hypogonadism, alcohol abuse, smoking, gastrointestinal disease, hypercalcium and immobilisation. Approximately 20% of symptomatic vertebral fractures, 25% of forearm fractures and 30% of hip fractures occur in men, and men have a higher incidence of hip and vertebral fractures following distal forearm fractures in comparison to women. These fractures have a profound impact on the individual in terms of morbidity and mortality, with 20% overall mortality in the first 12 months following hip fracture, with higher mortality rates in men than women. In England during 2011-2012, there were 4,341 hospital admissions for osteoporosis in men, 1,699 of which were with a pathological fracture.

First line therapy for osteoporosis usually involves treatment with bisphosphonates. Odanacatib is currently in one phase III clinical trial comparing its effect on bone mineral density against treatment with placebo. This trial is expected to complete in 2013.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.
TARGET GROUP

- Male osteoporosis: in patients who cannot tolerate, do not wish to persist with, do not respond to, or are contraindicated for oral bisphosphonate therapy – first and second line.

TECHNOLOGY

DESCRIPTION

Odanacatib (MK-0822) is an inhibitor of cathepsin K, a protease that is involved in the catabolism of elastin, collagen and gelatine. Abnormal cathepsin activity may result in bone disorders such as osteoporosis. Odanacatib treatment decreases bone resorption by selectively inhibiting the proteolysis of matrix protein by cathepsin K without affecting other osteoclast activities or osteoclast viability. Odanacatib is intended for the treatment of men with osteoporosis, either first line (in patients who have contraindications to oral bisphosphonates) or second line (in patients who cannot tolerate, do not wish to persist with, or who do not respond to oral bisphosphonate therapy). Odanacatib is administered orally at 50mg once weekly.

Odanacatib is in phase III clinical trials for post-menopausal osteoporosis and also in phase II clinical trials for bone metastases in patients with breast cancer.

INNOVATION and/or ADVANTAGES

If licensed, odanacatib will offer an additional oral treatment option for men with osteoporosis.

DEVELOPER

Merck Sharp & Dohme Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Osteoporosis is a progressive, systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporotic fractures are defined as fractures associated with low bone mineral density (BMD) and typically affect the spine, forearm, hip and shoulder.
NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

Osteoporosis is a common condition that affects 1 in 3 women and 1 in 5 men over the age of 50\(^3\), with a lifetime risk of fracture in this age group being estimated at 50% in women and 20-30% in men\(^4,5\). Nearly 75% of hip, spine and distal forearm fractures occur in patients ≥65 years\(^5\). Around 50% of men with osteoporosis have at least one secondary cause\(^a\), which most commonly include treatment with glucocorticoids, hypogonadism, alcohol abuse, smoking, gastrointestinal disease, hypercalciuria and immobilisation\(^6\). In England during 2011-2012, there were 4,341 hospital admissions for osteoporosis in men, 1,699 of which were with a pathological fracture\(^7\).

Approximately 20% of symptomatic vertebral fractures, 25% of forearm fractures and 30% of hip fractures occur in men\(^5\). Men have a higher incidence of hip and vertebral fractures following distal forearm fractures in comparison to women\(^9\). These fractures have a profound impact on the individual in terms of morbidity and mortality, with 20% overall mortality in the first 12 months following hip fracture, and higher mortality rates in men than women\(^5\). The mortality rate in men after hip fracture increases with age and over the first 6 months is approximately double that compared to similarly aged women\(^5\). Hip fracture permanently disables 50% of those affected and only 30% of patients fully recover\(^2\).

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance
- NICE clinical guideline. Osteoporosis: assessing the risk of fragility fracture (CG146). August 2012\(^2\).

Other Guidance
- National Osteoporosis Guideline Group. Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. 2010\(^9\).
- National Osteoporosis Foundation. Clinician’s guide to prevention and treatment of osteoporosis. 2010\(^10\).

\(^a\) Expert personal communication.
EXISTING COMPARATORS and TREATMENTS

Men who are found to have a high risk of fracture or who have already suffered a fragility fracture should normally be referred to specialist centres for assessment. The diagnosis of osteoporosis is typically more complex in men and some treatments are only licensed for use in post-menopausal women or men on corticosteroid therapy\(^15\). In addition to pharmacological treatments, patients may be given concurrent calcium and vitamin D supplements and advised to make lifestyle changes\(^16\).

Current licensed pharmacological treatment options for men include\(^{15,16,17}\):
- **Bisphosphonates**
  - Alendronate, 10mg daily.
  - Risedronate, 35mg once weekly.
  - Zoledronic acid (Aclasta), yearly intravenous (IV) administration.
- **Other medications**
  - Teriparatide, a recombinant fragment of human parathyroid hormone, SC administration.
  - Strontium ranelate (Protelos).
  - Hormone replacement therapy (testosterone) – for hypogonadal men; however this is associated with increased cardiovascular events and risk of prostate cancer in older men\(^b\).
  - Calcitriol.
  - Calcitonin – this is no longer used in the UK.

Although not licensed for use in men, alendronate (Fosamax 70mg once weekly) and ibandronate (Bonviva) are often prescribed, as is Preotact, another recombinant parathyroid hormone treatment\(^15\).

Efficacy and Safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01120600, EUCTR2010-019454-41-LV, MK0822-053; odanacatib vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Merck Sharp &amp; Dohme.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry(^18).</td>
</tr>
<tr>
<td>Location</td>
<td>Not reported.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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</tbody>
</table>

**Participants**
- n=266 (planned); aged 40-95 years; males; osteoporosis; ambulatory; suitable for dual energy x-ray absorptiometry scan; no fragility fractures in 12 months prior to study; no current treatment with oral bisphosphonates or other agents.

**Schedule**
- Randomised to odanacatib 50mg oral once weekly, or placebo oral once weekly, both with vitamin D3 5,600 IU once weekly and calcium carbonate.

\(^b\) Expert personal communication.
Follow-up | Active treatment period 24 months.
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Primary outcome | Lumbar spine bone mineral density (BMD).
Secondary outcomes | Total hip, femoral neck and trochanter BMD; serum C-telopeptide and urine N-telopeptide fraction of type 1 collagen.
Expected reporting date | Study completion date reported as Jul 2013.

**ESTIMATED COST and IMPACT**

**COST**

The cost of odanacatib is not yet known. The cost of other selected treatments for male osteoporosis are:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost for 1 year</th>
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</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>10mg once daily 70mg weekly oral tablet (unlicensed)</td>
<td>£18.72, £14.30</td>
</tr>
<tr>
<td>Risedronate</td>
<td>35mg weekly oral tablet</td>
<td>£248</td>
</tr>
<tr>
<td>Zoledronic acid (Aclasta)</td>
<td>5mg IV infusion over 15 mins once a year</td>
<td>£253</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>20µg daily SC</td>
<td>£3,262</td>
</tr>
</tbody>
</table>

**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
- Decreased use of existing services
- Re-organisation of existing services: Appropriate monitoring will be required, initially in the secondary sector in specialised units (endocrine or rheumatological).
- Need for new services
- Other: There is currently a difficulty in identifying at risk males and getting them onto treatment.
- None identified

Impact on Costs

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other: uncertain unit cost compared to existing treatments.
- None identified

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\[c\] Expert personal communication.
Clinical uncertainty or other research question identified: Expert opinion suggests that as the pathogenesis of male osteoporosis is different to that of women, further research is required to obtain anti-fracture data in addition to bone density, as a lack of fracture risk evidence is one of the main challenges clinicians face when choosing treatments for men. Expert opinion also suggests that comparator studies are required to inform the best choice of agents. Further research into optimum duration of therapy, appropriate treatments in renal failure and the efficacy of odanacatib in prostate cancer are also suggested. In addition, as poor long-term compliance is a problem with osteoporosis treatment, data on odanacatib compliance would also be useful. Expert opinion expresses uncertainty surrounding the proposed place of treatment for odanacatib; as 50% of males have secondary causes of osteoporosis, other treatments e.g. testosterone, may be more appropriate. As there is a lack of knowledge on how far testosterone replacement therapy benefits fracture risk in hypogonadal men, expert opinion suggests that these patients should be excluded from odanacatib trials and further research for hormone replacement therapy should be conducted.

REFERENCES