NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Non-bisphosphonates for treating osteoporosis

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of abaloparatide, denosumab raloxifene, romosozumab and teriparatide within their marketing authorisations for treating osteoporosis.

Background

Osteoporosis is a progressive skeletal disorder which is characterised by low bone mass and deterioration of the structure of bone tissue, leading to an increase in bone fragility and risk of fracture.

Osteoporosis is asymptomatic and often remains undiagnosed in the absence of fracture. In the UK, it is estimated that around 3 million people have osteoporosis, which is defined as having a bone mineral density (BMD) that is 2.5 standard deviations or more below the average value for young healthy adults (usually referred to as a 'T-score' of -2.5 or lower). The prevalence of osteoporosis increases markedly with age. In women, decreased oestrogen levels after the menopause accelerate bone loss, increasing the risk of osteoporosis. Half of women and one-fifth of men over the age of 50 will break a bone, mostly as a result of low bone strength.[1] Osteoporosis can also be caused by the long-term systemic use of corticosteroids.

There are approximately 536,000 new fragility fractures in the UK per year.[2] Osteoporotic fragility fractures occur most commonly in the hip, vertebrae and wrist. After a hip fracture, a high proportion of people are permanently unable to walk independently or to perform other activities of daily living and, consequently, many are unable to live independently. Vertebral fractures can be associated with curvature of the spine and height loss, and can result in chronic pain, breathing difficulties, gastrointestinal problems and difficulties in performing activities of daily living. Both hip and vertebral fractures are associated with increased mortality.

Currently, related NICE guidance includes:

- NICE clinical guideline 146, 'Osteoporosis: assessing the risk of fragility fracture', which recommends:
    - considering the assessment of fracture risk in all women aged 65 years and over and all men aged 75 years and over

  - considering the assessment of fracture risk in women aged under 65 years and men aged under 75 years in the presence of risk factors

  - not routinely assessing fracture risk in people aged under 50 years unless they have major risk factors (for example, current or frequent recent use of systemic corticosteroids, untreated premature menopause or previous fragility fracture)

  - estimating absolute fracture risk when assessing risk of fracture (for example, the predicted risk of major osteoporotic or hip fracture over 10 years, expressed as a percentage) using either FRAX[3] or QFracture.[4]

  See Appendix A for the full recommendations from NICE clinical guideline 146.

- NICE technology appraisal 464, which recommends oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium) and intravenous bisphosphonates (ibandronic acid and zoledronic acid) for treating osteoporosis in people who are eligible for risk assessment as defined in NICE's guideline on osteoporosis, depending on the person's risk of fragility fracture.

- NICE technology appraisal guidance 204, which recommends denosumab:

  - for the primary prevention of fragility fractures in postmenopausal women at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture, who have osteoporosis and cannot take alendronate

  - for the secondary prevention of osteoporotic fragility fractures in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.

- NICE technology appraisal guidance 161, which recommends raloxifene and strontium ranelate (currently discontinued), and teriparatide at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture, for women who have already sustained a fracture and who cannot take alendronate.

[3] FRAX, the World Health Organisation (WHO) fracture assessment tool, is available from www.shef.ac.uk/FRAX. It can be used for people aged between 40 and 90 years, either with or without BMD values, as specified.
[4] QFracture is available from www.qfracture.org. It can be used for people aged between 30 and 84 years. BMD values cannot be incorporated into the risk algorithm.

The review proposal[5]

In the previously published technology appraisal recommendations for preventing osteoporotic fragility fractures (NICE technology appraisal guidance 160, 161 and 204), intervention thresholds were defined using age, T-score and a number of risk factors, the latter being considered qualitatively. In NICE clinical guideline 146, risk is defined as absolute fracture risk, integrating all risk factors quantitatively. Following a stakeholder workshop, multiple technology appraisals (MTAs) were considered necessary to align NICE technology appraisal guidance on treatment with the NICE clinical guideline on risk assessment, to include new prices, to include other bisphosphonates for which guidance is needed, and to include guidance for treating men. It was decided to appraise:

- All relevant bisphosphonates licensed for the prevention of osteoporotic fragility fractures in women and men as an MTA, and that this should be given priority in scheduling (now published as NICE technology appraisal 464)

- All non-bisphosphonates licensed for the prevention of osteoporotic fragility fractures in women and men as an MTA, to be scheduled to begin when the MTA on bisphosphonates had published its final appraisal determination.

The MTA will consider people assessed for risk of fragility fracture according to the recommendations in clinical guideline 146. Identifying people at risk, and the impact of previous fracture on fracture risk are therefore considered clinical practice. This means that primary and secondary prevention will not need to be considered separately (apart from as risk factors). The NICE Decision Support Unit[6] carried out a feasibility study during the review proposal process which suggested that there were limitations to generating an algorithm, based only on absolute fracture risk (defined by either FRAX or Q Fracture), to robustly predict the cost effectiveness of interventions, and that these limitations could be overcome by using pragmatic and simplifying approaches.

The technologies

Abaloparatide (brand name unknown, Radius Health) is a synthetic peptide analogue of human parathyroid hormone-related protein that stimulates new bone formation. It is administered subcutaneously. Abaloparatide does not currently have a marketing authorisation in the UK for treating osteoporosis. It has been studied in clinical trials compared with placebo and compared with

[5] https://www.nice.org.uk/guidance/TA204/documents/ta204-osteoporotic-fractures-denosumab-review-decision-march-2014

[6] Stevenson, M. Assessing the feasibility of transforming the recommendations in ta160, ta161 and ta204 into absolute 10-year risk of fracture, NICE Decision Support Unit, May 2013. http://www.nice.org.uk/guidance/ta204/resources/ta204-technologies-for-the-primary-and-secondary-prevention-of-osteoporotic-fractures-appendix-c-decision-support-unit-report2

teriparatide for the prevention of fractures in postmenopausal women with severe osteoporosis.

Denosumab (Prolia, Amgen) is a monoclonal antibody that reduces osteoclast activity, and so reduces bone breakdown. It is administered as a single subcutaneous injection. Denosumab has a marketing authorisation in the UK for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures.

Raloxifene (Evista, Daiichi Sankyo) is a selective oestrogen receptor modulator. It is administered orally. Raloxifene has a marketing authorisation in the UK for the treatment and prevention of osteoporosis in postmenopausal women. Non-proprietary raloxifene (Sandoz, Consilient Health, Actavis UK, Mylan UK) is also available for the same indication.

Romosozumab (Evenity, UCB and Amgen) is a monoclonal antibody that inhibits the protein sclerostin, increasing bone formation and decreasing bone breakdown. It is administered as a subcutaneous injection. It does not currently have a marketing authorisation in the UK for treating osteoporosis. It has been studied in clinical trials compared with placebo, compared with teriparatide and compared with alendronate for treating osteoporosis in postmenopausal women. It has also been studied in a randomised, placebo-controlled clinical trial for treating osteoporosis in men.

Teriparatide (Forsteo, Eli Lilly) is a recombinant fragment of human parathyroid hormone and, as an anabolic agent, it stimulates formation of new bone and increases resistance to fracture. It is administered daily as a subcutaneous injection for up to 24 months. Teriparatide has a marketing authorisation in the UK for treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture.

Intervention(s)	Non-bisphosphonates (abaloparatide, denosumab raloxifene, romosozumab and teriparatide)
Population(s)	Adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146.
Comparators	• Bisphosphonates • Non-bisphosphonates compared with each other • No active treatment

Outcomes	The outcome measures to be considered include: • osteoporotic fragility fracture • bone mineral density • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Bisphosphonates for treating osteoporosis (2017). NICE technology appraisal 464. Review date August 2020. Related Guidelines: Osteoporosis: assessing the risk of fragility fracture (2017) NICE guideline CG146. Review date to be scheduled. Related Quality Standards: Osteoporosis (2017) NICE quality standard 149 Related NICE Pathways: Osteoporosis (2017) NICE pathway
Related National Policy	Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 2 and 5. https://www.gov.uk/government/publications/nhs-

	outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for the technologies been included in the scope?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom the technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider the technologies will fit into the existing NICE pathway, Osteoporosis?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the technologies are or will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

Do you consider the technologies to be innovative in their potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of the technologies can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the appraisal committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of these technologies into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)

References

1 National Osteoporosis Society (2017) Available at http://www.nos.org.uk/page.aspx?pid=328. Accessed November 2017.

2 National Osteoporosis Guideline Group (2017) Clinical guideline for the prevention and treatment of osteoporosis. Accessed November 2017.

APPENDIX A

Recommendations from NICE clinical guideline 146 'Osteoporosis: assessing the risk of fragility fracture'. The full guideline can be found at http://guidance.nice.org.uk/CG146/Guidance.

Targeting risk assessment

1.1 Consider assessment of fracture risk:

- In all women aged 65 years and over and all men aged 75 years and over
- in women aged under 65 years and men aged under 75 years in the presence of risk factors, for example:
  - previous fragility fracture
  - current use or frequent recent use of oral or systemic glucocorticoids
  - history of falls
  - family history of hip fracture
  - other causes of secondary osteoporosis
  - low body mass index (BMI) (less than 18.5 kg/m^2)
  - smoking
  - alcohol intake of more than 14 units per week for women and more than 21 units per week for men.

1.2 Do not routinely assess fracture risk in people aged under 50 years unless they have major risk factors (for example, current or frequent recent use of oral or systemic glucocorticoids, untreated premature menopause or previous fragility fracture), because they are unlikely to be at high risk.

Methods of risk assessment

1.3 Estimate absolute risk when assessing risk of fracture (for example, the predicted risk of major osteoporotic or hip fracture over 10 years, expressed as a percentage).

1.4 Use either FRAX (without a bone mineral density [BMD] value if a dual-energy X-ray absorptiometry [DXA] scan has not previously

been undertaken) or QFracture, within their allowed age ranges, to estimate 10-year predicted absolute fracture risk when assessing risk of fracture. Above the upper age limits defined by the tools, consider people to be at high risk.

1.5 Interpret the estimated absolute risk of fracture in people aged over 80 years with caution, because predicted 10-year fracture risk may underestimate their short-term fracture risk.

1.6 Do not routinely measure BMD to assess fracture risk without prior assessment using FRAX (without a BMD value) or QFracture.

1.7 Following risk assessment with FRAX (without a BMD value) or QFracture, consider measuring BMD with DXA in people whose fracture risk is in the region of an intervention threshold for a proposed treatment, and recalculate absolute risk using FRAX with the BMD value.

1.8 Consider measuring BMD with DXA before starting treatments that may have a rapid adverse effect on bone density (for example, sex hormone deprivation for treatment for breast or prostate cancer).

1.9 Measure BMD to assess fracture risk in people aged under 40 years who have a major risk factor, such as history of multiple fragility fracture, major osteoporotic fracture, or current or recent use of high-dose oral or high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer).

1.10 Consider recalculating fracture risk in the future:

- if the original calculated risk was in the region of the intervention threshold for a proposed treatment and only after a minimum of 2 years, **or**
- when there has been a change in the person's risk factors.

1.11 Take into account that risk assessment tools may underestimate fracture risk in certain circumstances, for example if a person:

- has a history of multiple fractures
- has had previous vertebral fracture(s)
- has a high alcohol intake
- is taking high-dose oral or high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer)
- has other causes of secondary osteoporosis.

1.12 Take into account that fracture risk can be affected by factors that may not be included in the risk tool, for example living in a care home or taking drugs that may impair bone metabolism (such as anti-convulsants, selective serotonin reuptake inhibitors, thiazolidinediones, proton pump inhibitors and anti-retroviral drugs).