NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Bisphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technology appraisal guidance 160 and 161)

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of alendronate, etidronate[1], risedronate, zoledronate and ibandronate, within their licensed indications, for the prevention of osteoporotic fragility fractures

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 England, it is estimated that more than 2.3 million people have osteoporosis, which is defined as having a bone mineral density (BMD) that is 2.5 standard deviations (SD) 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 both women and men. In women, decreased oestrogen levels after the menopause accelerate bone loss, increasing the risk of osteoporosis. In women and men osteoporosis can also be induced by the long-term systemic use of corticosteroids.

There are approximately 300,000 osteoporosis-related fractures in the UK per year. 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, which can result in chronic pain, breathing difficulties, gastrointestinal problems and difficulties in performing activities of daily living. It is thought that the majority of vertebral fractures (50–70%) do not come to clinical

[1] Etidronate (Didronel; Warner Chilcott) will not be included as an intervention in the appraisal, as it has been discontinued by its manufacturer in the UK.

attention. Both hip and vertebral fractures are associated with increased mortality.

Currently, related NICE guidance includes a clinical guideline for identifying women and men at risk of fracture and 3 technology appraisals of treatments for the prevention of fracture for post-menopausal women only.

NICE Clinical Guideline 146, 'Osteoporosis: assessing the risk of fragility fracture' recommends that assessment of fracture risk should be considered:

- in all women aged 65 years and over and all men aged 75 years and over; and

- 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.

NICE Clinical Guideline 146 also recommends that fracture risk should not be routinely assessed 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). It also states that absolute fracture risk should be estimated 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[2] or QFracture.[3] See Appendix A for the recommendations from NICE clinical guideline 146.

NICE technology appraisal guidance 160 recommends alendronate as first-line treatment for the primary prevention of fragility fractures in postmenopausal women with osteoporosis who have an increased fracture risk defined by age, T-score, and number of independent clinical risk factors for fracture, or indicators of low BMD. For women who cannot take alendronate, NICE technology appraisal guidance 160 and 204 recommend risedronate, etidronate, strontium ranelate or denosumab, at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture.

[2] 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.
[3] 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.

NICE technology appraisal guidance 161 (secondary prevention, in women who have already sustained a fracture) recommends alendronate for secondary prevention of fragility fractures in post-menopausal women with confirmed osteoporosis. For women who cannot take alendronate, NICE technology appraisal guidance 161 recommends risedronate, etidronate, raloxifene, strontium ranelate, and teriparatide at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture.

NICE technology appraisal guidance 204 recommends denosumab as a treatment option for the secondary prevention of osteoporotic fragility fractures only 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.

The review proposal[4]

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, 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 treatment in 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

- 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 has published its final appraisal determination

The MTA will consider those assessed for risk of fragility fracture according to the recommendations in clinical guideline 146. Identifying people at risk, and the impact of prior fracture on fracture risk, are therefore considered clinical

[4] NICE Review of TA160, 161 and 204; Technologies for the primary and secondary prevention of osteoporotic fractures. http://www.nice.org.uk/guidance/ta160/resources/ta160-technologies-for-the-primary-and-secondary-prevention-of-osteoporotic-fractures-appendix-b-proposal-paper-presented-to-the-institutes-guidance-executive2

practice and primary and secondary prevention will not need to be considered separately (apart from as risk factors). The first MTA will develop the framework to link absolute fracture risk with intervention thresholds, based on cost effectiveness. The NICE Decision Support Unit[5] 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. This MTA will establish the acceptability of such simplifying approaches.

The technologies

Alendronate (Fosamax, Fosamax Once Weekly and Fosavance [co-formulation with cholecalciferol], MSD) has a UK marketing authorisation for treating postmenopausal osteoporosis, orally once daily or weekly. It also has a UK marketing authorisation for treating osteoporosis in men and for preventing and treating corticosteroid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy, orally once daily. Non-proprietary alendronate (AAH, Accord, Actavis, Alliance Healthcare, Almus, Apotex UK, Fannin UK, Focus, Generics UK, Kent, Mylan UK, Phoenix Healthcare Distribution, PLIVA, Ranbaxy, Rosemont, Somex, Sun, Teva UK, Waymade, Wockhardt and Zentiva) also has a UK marketing authorisation for the same indications.

Ibandronate (Bonviva, Roche) has a UK marketing authorisation for treating postmenopausal osteoporosis, orally once monthly or every 3 months by intravenous injection. Non-proprietary ibandronate (Actavis UK, Consilient Health, Mylan UK, Sun and Teva UK) also has a UK marketing authorisation for the same indications.

Risedronate (Actonel and Actonel Once a Week, Warner Chilcott) has a UK marketing authorisation for treating postmenopausal osteoporosis to reduce risk of vertebral or hip fractures, orally once daily or weekly. It has a marketing authorisation for preventing osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women, orally once daily, and for treating osteoporosis in men at high risk of fractures, orally once weekly. Non-proprietary risedronate (AAH, Actavis, Alliance Healthcare, Aspire, Aurobindo, Bluefish, Dr Reddy's Laboratories, Mylan UK, Phoenix Healthcare Distribution, Ranbaxy, Sandoz, Sovereign Medical, Teva UK, and Zentiva) also has a UK marketing authorisation for the same indications.

[5] 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

Zoledronate (Aclasta, Novartis) has a UK marketing authorisation for treating postmenopausal osteoporosis and osteoporosis in men (including corticosteroid-induced osteoporosis) by intravenous infusion once a year. Generic zoledronate does not have a UK marketing authorisation for treating osteoporosis. Non-proprietary zelondronate (SUN Pharmaceuticals) also has a UK marketing authorisation for the same indications.

Etidronate (Didronel; Warner Chilcott) is not included as an intervention in this scope. It has a UK marketing authorisation for the prevention and treatment of corticosteroid-induced osteoporosis, but it has been discontinued by its manufacturer in the UK.

Intervention(s)	Bisphosphonates (alendronate, ibandronate, risedronate and zoledronate)
Population(s)	Adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146
Comparators	• Bisphosphonates will be 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.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. If evidence allows, subgroups based on patient characteristics that increase the risk of fracture (that is, those specified in NICE clinical guideline 146) or that affect the impact of fracture on lifetime costs and outcomes should be considered. If evidence allows, the impact of treatment duration and adherence on costs and outcomes will be considered.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 161, Oct 2008, 'Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women'. Technology Appraisal No. 160, Oct 2008, 'Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women' Related Guidelines: Clinical Guideline No. 146, Aug 2012, 'Osteoporosis: assessing the risk of fragility fracture, Review Proposal Date Aug 2015. Related NICE Pathways NICE Pathway: Osteoporosis, Pathway created: Aug 2012. http://pathways.nice.org.uk/
Related National Policy	http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf

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[7]
  - 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).