

**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)**

**Draft scope**

**Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of bisphosphonates (alendronate, ibandronate, risedronate and zoledronate) within their licensed indications for preventing 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 attention. Both hip and vertebral fractures are associated with increased mortality.

National Institute for Health and Care Excellence

Draft scope for the appraisal of bisphosphonates for preventing osteoporotic fragility fractures (partial update of NICE technology appraisal guidance 160 and 161)

Currently, related NICE guidance includes a clinical guideline for identifying women and men at risk of fracture and 3 technology appraisals of treatments 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<sup>2</sup>), smoking, alcohol intake of more than 14 units per week for women and more than 21 units per week for men.

The guideline 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; see Appendix A). 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<sup>1</sup> or QFracture.<sup>2</sup> 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, teriparatide or denosumab, at specified fracture risks, defined by age, T-score and number of independent clinical risk factors for fracture.

NICE technology appraisal guidance 161 (secondary prevention, in women who have already sustained a fracture) recommends alendronate for

---

<sup>1</sup> FRAX, the World Health Organisation (WHO) fracture assessment tool, is available from [www.shef.ac.uk/FRAX](http://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.

<sup>2</sup> QFracture is available from [www.qfracture.org](http://www.qfracture.org). It can be used for people aged between 30 and 84 years. BMD values cannot be incorporated into the risk algorithm.

secondary prevention of fragility fractures in post-menopausal women with confirmed osteoporosis. For women who cannot take alendronate, NICE technology appraisal guidance 160 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**

In the previously published technology appraisal recommendations on osteoporosis treatments (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, NICE decided an MTA was needed 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. This MTA will also develop the framework to link absolute fracture risk with intervention thresholds, based on cost effectiveness.

### **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

National Institute for Health and Care Excellence

Draft scope for the appraisal of bisphosphonates for preventing osteoporotic fragility fractures (partial update of NICE technology appraisal guidance 160 and 161)

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.

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.

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

<b>Intervention(s)</b>	Bisphosphonates (alendronate, ibandronate, risedronate and zoledronate)
<b>Population(s)</b>	Adults at increased absolute risk of osteoporotic fracture, identified by applying the recommendations in NICE clinical guideline 146
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• Bisphosphonates will be compared with each other</li> <li>• No active treatment</li> </ul>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• osteoporotic fragility fracture</li> <li>• bone mineral density</li> <li>• treatment adherence</li> </ul>

National Institute for Health and Care Excellence

Draft scope for the appraisal of bisphosphonates for preventing osteoporotic fragility fractures (partial update of NICE technology appraisal guidance 160 and 161)

	<ul style="list-style-type: none"> <li>• mortality</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>
<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>
<b>Other considerations</b>	Guidance will only be issued in accordance with the marketing authorisation.
<b>Related NICE recommendations and NICE Pathways</b>	<p>Related Technology Appraisals:</p> <p>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'.</p> <p>Technology Appraisal No. 160, Oct 2008, 'Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women'</p> <p>Related Guidelines:</p> <p>Clinical Guideline No. 146, Aug 2012, 'Osteoporosis: assessing the risk of fragility fracture, Review Proposal Date Aug 2015.</p> <p>Related NICE Pathways</p> <p>NICE Pathway: Osteoporosis, Pathway created: Aug 2012. <a href="http://pathways.nice.org.uk/">http://pathways.nice.org.uk/</a></p>
<b>Related National Policy</b>	<a href="http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf">http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf</a>

National Institute for Health and Care Excellence

Draft scope for the appraisal of bisphosphonates for preventing osteoporotic fragility fractures (partial update of NICE technology appraisal guidance 160 and 161)

### Questions for consultation

In 2012, NICE Clinical Guideline 146 recommended FRAX or QFracture as the main tools for assessing fracture risk. Since then, have any other tools become established in clinical practice? Are any other tools, or factors, considered similarly important for decision making? If so, what are they?

Have all relevant comparators for bisphosphonates and manufacturers been included in the scope? Should calcium and vitamin D supplements be included as comparators?

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

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 treatments are 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 technologies;
- 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 that the use of these 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.

Where do you consider these technologies will fit into the existing NICE [Osteoporosis](#) pathway?

National Institute for Health and Care Excellence

Draft scope for the appraisal of bisphosphonates for preventing osteoporotic fragility fractures (partial update of NICE technology appraisal guidance 160 and 161)

## 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<sup>[7]</sup>
  - low body mass index (BMI) (less than 18.5 kg/m<sup>2</sup>)
  - 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).