

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA160, 161 and 204; Technologies for the primary and secondary prevention of osteoporotic fractures¹

TA160 and TA161 give guidance on alendronate, risedronate, etidronate, strontium ranelate, raloxifene and teriparatide, and were re-issued after the Judicial Review in January 2011. TA204 gives guidance on denosumab and was issued in October 2010. TA160 and TA161 were to be considered for review after the short clinical guideline on risk assessment has been published. TA204 was to be considered for review at the same time that TA160 and TA161 are considered for review.

In August 2012 the clinical guideline on [assessing the risk of fragility fractures in people with osteoporosis](#) was published (CG146).

In July 2012 Guidance Executive agreed to reschedule the review proposal for the above technology appraisals so that we can explore how treatment intervention thresholds from the technology appraisals can be aligned to the assessment of absolute fracture risk recommended in CG146, and to carry out a feasibility study through NICE's Decision Support Unit.

¹ Review of TA160; Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women, TA161; Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, and TA204; Denosumab for the prevention of osteoporotic fractures in postmenopausal women.

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1. Recommendation

To develop an implementation tool that allows the recommendations from TA160, 161 and 204 to be expressed in line with the recommendations for risk assessment in the short clinical guideline (CG146), without a full review of the evidence for bisphosphonates, raloxifene or teriparatide in post-menopausal women.

To combine this with the recently referred appraisal of drugs for osteoporosis treatment in men.

That we consult on this proposal, and hold an exploratory workshop to discuss responses received in consultation. This workshop will include stakeholders and other NICE guidance producing centres to explore the best way to support the development of the underpinning evidence base for the forthcoming NICE quality standard.

2. Original remit(s)

TA160, TA161:

To establish the clinical and cost effectiveness of selective oestrogen receptor modulators (SERMs), bisphosphonates, and parathyroid hormone (subject to licensing) for the prevention and treatment of osteoporosis and the prevention of osteoporotic fractures in post-menopausal women.

TA204:

To produce a technology appraisal on the clinical and cost effectiveness of denosumab for the treatment and prevention of osteoporosis (post-menopausal).

3. Summary of current guidance

In TAs160, 161 and 204 the recommendations for the individual drugs specify age and T-score and a number of risk factors. Alendronate is recommended as the first line treatment for both primary and secondary prevention, and the other interventions are recommended for people who cannot take alendronate, and who are higher risk of fracture (reflecting the cost effectiveness of each drug).

See appendix 1 for full guidance sections.

4. Rationale²

In the previously published technology appraisal recommendations on osteoporosis treatments, intervention thresholds were defined using age, T-score and a number of risk factors, the latter being considered qualitatively. The clinical guideline on risk

² A list of the options for consideration, and the consequences of each option is provided in Appendix 4 at the end of this paper

assessment (CG146³) was published in August 2012 and recommends the use of absolute fracture risk for risk assessment, integrating all risk factors quantitatively. Therefore, it is desirable for NICE recommendations on treatment decisions to be aligned with the recommendations on risk assessment. The development of an approach that aligns the technology appraisals with CG146 would be more efficient than a full review of the appraisals, which would take a lot of resource and time to develop. Also, the various licence extensions for osteoporosis treatments, and the new clinical evidence and the majority of the safety data are not expected to lead to considerably different recommendations. The first line treatment recommended in the technology appraisals, alendronate, is now available at an extremely low annual treatment cost. For these reasons, a full update of the guidance is not considered a good use of NICE resources.

The Department of Health has referred a multiple technology appraisal of drugs for the treatment of osteoporosis in men to NICE with the remit *'to appraise the clinical and cost effectiveness of alendronate, denosumab, risedronate, strontium ranelate, teriparatide and zoledronic acid⁴ within their licensed indications for the prevention of osteoporotic fractures in men⁵*.

The marketing authorisations for treatment in men are based on bridging studies. Such studies are considered sufficient for granting a marketing authorisation with the indication "treatment of osteoporosis in men at increased risk of fracture" provided that: the duration of the study is at least one year; the dosage is justified, and the manufacturer justifies that the cut-off of BMD, age and any other risk factor chosen for the inclusion of men in the pivotal study will generate a fracture risk of a similar magnitude compared with postmenopausal women that were recruited in the studies used to obtain the indication for treatment of postmenopausal osteoporosis in women, and the magnitude of the changes in BMD versus placebo is similar to that observed in postmenopausal osteoporotic women treated with the same compound and is proportional to the decreased incidence of fractures in treated women. Therefore, efficacy data for fracture outcomes in men is not available for all treatments. It has also been suggested that the risk of hip and vertebral fracture is similar in men and women for any given BMD. It is therefore likely that the assessment of cost effectiveness of treatments for osteoporosis in men will largely be based on studies in postmenopausal women.

Consideration of the clinical and cost effectiveness of these technologies in men at the same time as considering an approach to align the technology appraisals with

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<http://www.nice.org.uk/Search.do?searchText=risk+assessment+osteoporosis&newsearch=true&x=16&y=10#/search/?reload>

⁴ Should the proposed approach be approved a referral from the DH for the appraisal of zoledronic acid in postmenopausal women will be sought.

⁵ For the draft scope of this topic, please see: ;

<http://www.nice.org.uk/ourguidance/niceguidancebytype/technologyappraisals/proposedappraisals/nowave.jsp?domedia=1&mid=B02509CE-03BA-709C-DBF8E291340B6BC6>

CG146, without a full review of the evidence for the previously appraised technologies in post-menopausal women, would allow for an efficient use of technology appraisal resources, and is likely to result in better and comprehensive guidance to the NHS.

5. Implications for other guidance producing programmes

In August 2012 the clinical guideline CG146 was published on the risk assessment of fragility fractures in people with or at risk of osteoporosis. The guideline recommends the use of FRAX or QFracture for the estimation of absolute fracture risk. The guideline recommendations refer to intervention thresholds, but without cross referring to the published technology appraisals, as in the latter the recommendations are not presented as absolute fracture risk. The guideline included all people at risk of osteoporotic fragility fracture and specifies that drugs to prevent fractures will not be covered as they will be covered within future guidance produced by the Institute.

The development of a quality standard in osteoporosis has been referred to NICE. Other NICE guidance producing centres need to be included in the scoping of any review or update to the current technology appraisals to explore the best way to support the development of the underpinning evidence base for the forthcoming quality standard.

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from September 2009 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

For the new evidence see Appendix 2

8. Development of a tool to translate the appraisal recommendations into absolute risk

A full update of TA160, 161 and 204 would be a large and complex piece of work taking a lot of resource and time to develop. This would mean that the NHS would have to wait for a long time until CG146 and the technology appraisals are aligned.

There are some changes in the evidence, and particularly with the pricing of alendronate (see appendix 2). Because generic alendronate is now available at very low prices, the resources needed for the identification of people at risk would even more outbalance the cost of treatment. It is therefore not felt that a full update of the recommendations would provide benefit for the NHS.

However, it is important to explore an approach that describes the recommendations, i.e. treatment intervention thresholds, in a way that aligns them to the assessment of absolute fracture risk. To develop such an approach would take

considerably less time and would serve the immediate need of the NHS in reconciling the different pieces of NICE guidance.

It is necessary that the methodology underpinning any such approach involves a consultation with stakeholders, and that the Appraisal Committee recommends this tool in the context of the existing guidance.

As a first step towards exploring this approach, a feasibility study was carried out through NICE's Decision Support Unit (DSU). The DSU was asked to establish

1. the absolute risk values (hip and other osteoporotic fractures) for the groups of people for whom alendronate is recommended in TA160/1 using the risks derived from the model used in TA160/1 and derived from FRAX .
2. how the 10 year risks resulting from FRAX can be aligned with the annual risks used in the algorithm underpinning the TA development?

The results showed that that the fracture risks used in the modelling carried out for the development of TA160 and 161 highly correlate with the fracture risks that can be calculated with FRAX (see enclosed DSU report).

As a second step, the absolute risks were calculated using FRAX for major fracture and for hip fracture at which alendronate and risedronate were recommended in TA160 and TA161 (see enclosed DSU report).

The analysis of the absolute fracture risks where treatment was, and was not, recommended according to TA160 and TA161 showed some inconsistencies. The results show that the intervention thresholds vary depending on age and number of risk factors, and also between primary and secondary prevention. Part of this variation is a consequence of the recommendations being specified for T score of - 2.5 or below, part of the variation is a consequence of the fact that factors other than absolute fracture risk determine the cost effectiveness of the interventions.

However, a pragmatic way forward may be to use minimum fracture risk levels at which treatment can be recommended for the interventions included in the technology appraisals. Such approach would require the acceptance of some simplifying assumptions and decision rules, but would be a more efficient way of aligning the current NICE technology appraisal recommendations with the Clinical Guideline recommendations.

9. Implementation

A submission from Implementation is included in Appendix 5.

Based on the implementation advice received, there is some evidence that NICE guidance has influenced uptake or reduced use as expected from the guidance in TA160, TA161 and TA204. However, a 2010 audit found that only 67/171 commissioning organisations reported a mechanism to assess compliance with TA161.

10. Equality issues

In TA160/161 and TA204, the Committees carefully considered the position of women who cannot take alendronate because of a condition which either makes

alendronate contraindicated or which prevents individuals from complying with the instructions for administration for alendronate. In doing so the Committee noted that at least some women in this patient group were likely to be 'disabled' as defined by the Disability Discrimination Act 1995. The Committee concluded that all reasonable steps should be taken to provide women who have a disability that makes it difficult for them to comply with the instructions for administration of alendronate, with such practical support and assistance with administration (for example through district nurse visits or other home support services), as will enable them to take the drug. The Committee took the view that recommending drugs other than alendronate using the same criteria as alendronate for women who cannot take alendronate would not be justified in this case because of the very high ICERs for the alternative drugs.

Because the technologies included in this review have hugely different list prices, it is expected that intervention thresholds for the individual technologies will differ from each other, i.e. if one drug cannot be used for reasons of intolerance or contraindication, another may not be recommended at the same level of fracture risk.

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Appendix 1 Current guidance

TA160:

This guidance relates only to treatments for the primary prevention of fragility fractures in postmenopausal women who have osteoporosis. Osteoporosis is defined by a T-score⁶ of -2.5 standard deviations (SD) or below on dual-energy X-ray absorptiometry (DXA) scanning. However, the diagnosis may be assumed in women aged 75 years or older if the responsible clinician considers a DXA scan to be clinically inappropriate or unfeasible.

This guidance assumes that women who receive treatment have an adequate calcium intake and are vitamin D replete. Unless clinicians are confident that women who receive treatment meet these criteria, calcium and/or vitamin D supplementation should be considered.

NICE is developing a clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' (see www.nice.org.uk). This technology appraisal guidance should be read in the context of the clinical guideline when it is available.

This guidance does **not** cover the following:

- The treatment of women who have sustained a clinically apparent osteoporotic fragility fracture (for recommendations for the treatment of women with a prior osteoporotic fragility fracture, see the accompanying NICE technology appraisal, 'Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women').
- The use of alendronate, etidronate, risedronate, raloxifene or strontium ranelate for the primary prevention of osteoporotic fragility fractures in women with normal bone mineral density (BMD) or osteopenia (that is, women with a T-score between -1 and -2.5 SD below peak BMD).
- The use of these drugs for the primary prevention of osteoporotic fragility fractures in women who are on long-term systemic corticosteroid treatment.

The latter two groups will be covered within future guidance produced by the Institute.

1.1 Alendronate is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in the following groups:

⁶ T-score relates to the measurement of bone mineral density (BMD) using central (hip and/or spine) DXA scanning, and is expressed as the number of standard deviations (SD) from peak BMD.

- Women aged 70 years or older who have an independent clinical risk factor for fracture (see section 1.5) or an indicator of low BMD (see section 1.6) and who are confirmed to have osteoporosis (that is, a T-score of -2.5 SD or below). In women aged 75 years or older who have two or more independent clinical risk factors for fracture or indicators of low BMD, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.
- Women aged 65–69 years who have an independent clinical risk factor for fracture (see section 1.5) and who are confirmed to have osteoporosis (that is, a T-score of -2.5 SD or below).
- Postmenopausal women younger than 65 years who have an independent clinical risk factor for fracture (see section 1.5) and at least one additional indicator of low BMD (see section 1.6) and who are confirmed to have osteoporosis (that is, a T-score of -2.5 SD or below).

When the decision has been made to initiate treatment with alendronate, the preparation prescribed should be chosen on the basis of the lowest acquisition cost available.

1.2 Risedronate and etidronate are recommended as alternative treatment options for the primary prevention of osteoporotic fragility fractures in postmenopausal women:

- who are unable to comply with the special instructions for the administration of alendronate, or have a contraindication to or are intolerant of alendronate (as defined in section 1.7) **and**
- who also have a combination of T-score, age and number of independent clinical risk factors for fracture (see section 1.5) as indicated in the following table.

T-scores (SD) at (or below) which risedronate or etidronate is recommended when alendronate cannot be taken

Age (years)	Number of independent clinical risk factors for fracture (see section 1.5)		
	0	1	2
65–69	– ^a	–3.5	–3.0
70–74	–3.5	–3.0	–2.5
75 or older	–3.0	–3.0	–2.5

^a Treatment with risedronate or etidronate is not recommended.

If a woman aged 75 years or older who has two or more independent clinical risk factors for fracture or indicators of low BMD has not previously had her BMD measured, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.

In deciding between risedronate and etidronate, clinicians and patients need to balance the overall proven effectiveness profile of the drugs against their tolerability and adverse effects in individual patients.

1.3 Strontium ranelate is recommended as an alternative treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women:

- who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate (as defined in section 1.7) **and**
- who also have a combination of T-score, age and number of independent clinical risk factors for fracture (see section 1.5) as indicated in the following table.

T-scores (SD) at (or below) which strontium ranelate is recommended when alendronate and either risedronate or etidronate cannot be taken

Age (years)	Number of independent clinical risk factors for fracture (section 1.5)		
	0	1	2
65–69	– ^a	–4.5	–4.0
70–74	–4.5	–4.0	–3.5
75 or older	–4.0	–4.0	–3.0

^aTreatment with strontium ranelate is not recommended.

1.4 Raloxifene is not recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women.

1.5 For the purposes of this guidance, independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.

1.6 For the purposes of this guidance, indicators of low BMD are low body mass index (defined as less than 22 kg/m²), medical conditions such as ankylosing spondylitis, Crohn’s disease, conditions that result in prolonged immobility, and untreated premature menopause⁷.

1.7 For the purposes of this guidance, intolerance of alendronate, risedronate or etidronate is defined as persistent upper gastrointestinal disturbance that is

⁷ Rheumatoid arthritis is also a medical condition indicative of low BMD.

sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly.

1.8 For the purposes of this guidance, primary prevention refers to opportunistic identification, during visits to a healthcare professional for any reason, of postmenopausal women who are at risk of osteoporotic fragility fractures and who could benefit from drug treatment. It does not imply a dedicated screening programme.

1.9 Women who are currently receiving treatment with one of the drugs covered by this guidance, but for whom treatment would not have been recommended according to sections 1.1 to 1.4, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

TA161:

This guidance relates only to treatments for the secondary prevention of fragility fractures in postmenopausal women who have osteoporosis and have sustained a clinically apparent osteoporotic fragility fracture. Osteoporosis is defined by a T-score⁸ of -2.5 standard deviations (SD) or lower on dual-energy X-ray absorptiometry (DXA) scanning. However, the diagnosis may be assumed in women aged 75 years or older if the responsible clinician considers a DXA scan to be clinically inappropriate or unfeasible.

This guidance assumes that women who receive treatment have an adequate calcium intake and are vitamin D replete. Unless clinicians are confident that women who receive treatment meet these criteria, calcium and/or vitamin D supplementation should be considered.

NICE is developing a clinical guideline on 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' (see www.nice.org.uk). This technology appraisal guidance should be read in the context of the clinical guideline when it is available.

⁸ T-score relates to the measurement of bone mineral density (BMD) using central (hip and/or spine) DXA scanning and is expressed as the number of standard deviations (SD) from peak BMD.

This guidance does **not** cover the following:

- The use of alendronate, etidronate, risedronate, raloxifene, strontium ranelate or teriparatide for the secondary prevention of osteoporotic fragility fractures in women with normal bone mineral density (BMD) or osteopenia (that is, women with a T-score between -1 and -2.5 SD below peak BMD).
- The use of these drugs for the secondary prevention of osteoporotic fragility fractures in women who are on long-term systemic corticosteroid treatment.

These groups will be covered within future guidance produced by the Institute.

1.1 Alendronate is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis (that is, a T-score of -2.5 SD or below). In women aged 75 years or older, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.

When the decision has been made to initiate treatment with alendronate, the preparation prescribed should be chosen on the basis of the lowest acquisition cost available.

1.2 Risedronate and etidronate are recommended as alternative treatment options for the secondary prevention of osteoporotic fragility fractures in postmenopausal women:

- who are unable to comply with the special instructions for the administration of alendronate, or have a contraindication to or are intolerant of alendronate (as defined in section 1.6) **and**
- who also have a combination of T-score, age and number of independent clinical risk factors for fracture (see section 1.5) as indicated in the following table.

T-scores (SD) at (or below) which risedronate or etidronate is recommended when alendronate cannot be taken

Age (years)	Number of independent clinical risk factors for fracture (section 1.5)		
	0	1	2
50–54	$-^a$	-3.0	-2.5

55–59	–3.0	–3.0	–2.5
60–64	–3.0	–3.0	–2.5
65–69	–3.0	–2.5	–2.5
70 or older	–2.5	–2.5	–2.5

^a Treatment with risedronate or etidronate is not recommended

If a women aged 75 years or older has not previously had her BMD measured, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.

In deciding between risedronate and etidronate, clinicians and patients need to balance the overall proven effectiveness profile of the drugs against their tolerability and adverse effects in individual patients.

1.3 Strontium ranelate and raloxifene are recommended as alternative treatment options for the secondary prevention of osteoporotic fragility fractures in postmenopausal women:

- who are unable to comply with the special instructions for the administration of alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate (as defined in section 1.6) **and**
- who also have a combination of T-score, age and number of independent clinical risk factors for fracture (see section 1.5) as indicated in the following table.

T-scores (SD) at (or below) which strontium ranelate or raloxifene is recommended when alendronate and either risedronate or etidronate cannot be taken

Age (years)	Number of independent clinical risk factors for fracture (section 1.5)		
	0	1	2
50–54	– ^a	–3.5	–3.5
55–59	–4.0	–3.5	–3.5
60–64	–4.0	–3.5	–3.5
65–69	–4.0	–3.5	–3.0
70–74	–3.0	–3.0	–2.5
75 or older	–3.0	–2.5	–2.5

^a Treatment with raloxifene or strontium ranelate is not recommended

If a woman aged 75 years or older who has one or more independent clinical risk factors for fracture or indicators of low BMD has not previously had her BMD measured, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.

For the purposes of this guidance, indicators of low BMD are low body mass index (defined as less than 22 kg/m²), medical conditions such as ankylosing spondylitis, Crohn's disease, conditions that result in prolonged immobility, and untreated premature menopause⁹.

In deciding between strontium ranelate and raloxifene, clinicians and patients need to balance the overall proven effectiveness profile of these drugs against their tolerability and other effects in individual patients.

1.4 Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women:

- who are unable to take alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate (as defined in section 1.6), **or** who have a contraindication to, or are intolerant of strontium ranelate (as defined in section 1.7), **or** who have had an unsatisfactory response (as defined in section 1.8) to treatment with alendronate, risedronate or etidronate **and**
- who are 65 years or older and have a T-score of -4.0 SD or below, or a T-score of -3.5 SD or below plus more than two fractures, **or** who are aged 55–64 years and have a T-score of -4 SD or below plus more than two fractures.

1.5 For the purposes of this guidance, independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.

⁹ Rheumatoid arthritis is also a medical condition indicative of low BMD.

1.6 For the purposes of this guidance, intolerance of alendronate, risedronate or etidronate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly.

1.7 For the purposes of this guidance, intolerance of strontium ranelate is defined as persistent nausea or diarrhoea, either of which warrants discontinuation of treatment.

1.8 For the purposes of this guidance, an unsatisfactory response is defined as occurring when a woman has another fragility fracture despite adhering fully to treatment for 1 year and there is evidence of a decline in BMD below her pre-treatment baseline.

1.9 Women who are currently receiving treatment with one of the drugs covered by this guidance, but for whom treatment would not have been recommended according to sections 1.1 to 1.4, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

TA204:

1.1 Denosumab is recommended as a treatment option for the primary 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 **and**
- who have a combination of T-score¹, age and number of independent clinical risk factors for fracture (see section 1.3) as indicated in the following table.

T-scores (SD) at (or below) which denosumab is recommended when alendronate and either risedronate or etidronate are unsuitable

Age (years)	Number of independent clinical risk factors for fracture		
	0	1	2
65–69	– a	–4.5	–4.0

70–74	-4.5	-4.0	-3.5
75 or older	-4.0	-4.0	-3.0

^a Treatment with denosumab is not recommended.

1.2 Denosumab is recommended 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.

1.3 For the purposes of this guidance, independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.

1.4 People currently receiving denosumab for the primary or secondary prevention of osteoporotic fragility fractures who do not meet the criteria specified in recommendations 1.1 or 1.2 should have the option to continue treatment until they and their clinician consider it appropriate to stop.

Appendix 2 - Evidence and implications for review

Marketing authorisation and net price changes¹⁰

The UK marketing authorisations and net prices for raloxifene (Evista; Daiichi Sankyo) have not changed: 60 mg per tab, £17.06 for a 28-tab pack and £59.59 84-tab pack (annual cost £222.39 and £258.93, respectively).

Strontium ranelate (Protelos; Servier) has received an extension to the UK marketing authorisation to include the treatment of osteoporosis in adult men at increased risk of fracture. The net price has increased since publication of NICE guidance 160, from £25.60 to £27.08 for 28 sachets containing 2 grams (annual cost 353.01).

Denosumab (Prolia; Amgen) has received an extension to the UK marketing authorisation to include bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and the treatment of osteoporosis in men. The list price has not changed: £183 for a 1 ml pre-filled syringe, 60 mg per ml solution (annual cost £366).

Etidronate (Didronel; Warner Chilcott) has received an extension to the UK marketing authorisation for the prevention and treatment of corticosteroid-induced osteoporosis, but the manufacturer has since discontinued the product.

Proprietary once-daily alendronate (Fosamax; MSD) has remained priced at £23.12 for a 28-tab pack of 10 mg tablets (annual cost £301.39) and has received an extension to the UK marketing authorisation to include the treatment of osteoporosis in men to prevent fractures, for the treatment of glucocorticoid-induced osteoporosis and prevention of bone loss in post-menopausal women considered at risk of developing the disease. Non-proprietary once-daily alendronate has reduced in price from £8.30 to £1.45 for a 28-tab pack of 10 mg tablets (annual cost £18.90).

Proprietary once-weekly alendronate (Fosamax Once Weekly; MSD) has remained priced at £22.80 for a 4-tab pack of 70 mg tablets (annual cost £296.40) and is indicated for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. Non-proprietary once-weekly alendronate has reduced in price from £4.12 to £0.91 for a 4-tab pack of 70 mg tablets (annual cost £11.83). There is also a new formulation of non-proprietary alendronate which is a once-weekly oral solution in four 100 mL vials containing 70 mg of alendronate priced at £22.80 (annual cost £296.40).

Proprietary once-weekly alendronate with colecalciferol (Fosavance; MSD) has a UK marketing authorisation for the treatment of postmenopausal osteoporosis in women at risk of vitamin D insufficiency to reduce the risk of vertebral and hip fractures. It is priced at £22.80 for a 4-tab pack of 70 mg of alendronate with 70 micrograms of colecalciferol (annual cost £296.40).

¹⁰ All prices based on BNF online edition, July 2013 (excluding VAT).

Once-daily risedronate (Actonel; Warner Chilcott) has received an extension to the UK marketing authorisation to include the prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis and for maintaining or increasing bone mass in postmenopausal women undergoing long-term (more than 3 months) systemic corticosteroid treatment at doses greater than 7.5 mg of prednisone (or equivalent) per day. The price of once-daily risedronate has been reduced from £19.10 to £17.99 for a 28-tab pack of 5 mg tablets (annual cost £234.51).

Once-weekly risedronate (Actonel Once a Week; Warner Chilcott) has received an extension to the UK marketing authorisation to include the treatment of osteoporosis in men at high risk of fractures. The list price of once-weekly risedronate has been reduced from £20.30 to £19.12 for a 4-tab pack of 35 mg tablets (annual cost £248.56)

The price of non-proprietary risedronate is £13.59 for a 28-tab pack of once-daily 5 mg tablets and £1.20 for a 4-tab pack of once-weekly 35 mg tablets (annual cost £177.16 and £15.60, respectively).

A new formulation of once-weekly proprietary risedronate with calcium carbonate and colecalciferol (Actonel Combi, Warner Chilcott) has since received UK marketing authorisation for the treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures. The formulation contains a 4-tab pack of once-weekly 35 mg tablets of risedronate and 24 sachets containing 2.5 g of calcium carbonate and 22 micrograms of colecalciferol. The formulation costs £19.12 (annual cost £248.56).

Teriparatide (Forsteo; Eli Lilly) has received an extension to the UK marketing authorisation to include the treatment of osteoporosis in men at increased risk of fracture and for the treatment of glucocorticoid-induced osteoporosis in women and men at increased risk for fracture. The price for teriparatide has remained the same: £271.88 for a 28-day pre-filled pen with 2.4 ml at 250 micrograms per ml (annual cost £3544.15).

Several new interventions are currently in development for the primary and secondary prevention of osteoporosis in women, but have not yet received UK marketing authorisation.

Table 1 Summary of prices and indication changes for osteoporosis treatments

Technology	Brand	Manufacturer	Indication (bold indicates new indication since TA160,161 or 204)	Dose / schedule	Preparation	Original price	Current price	Current Annual price
Alendronate	Fosamax	MSD	<ul style="list-style-type: none"> • treatment of osteoporosis in men and post-menopausal women to prevent fractures • treatment of glucocorticoid-induced osteoporosis • prevention of bone loss in post-menopausal women considered at risk of developing osteoporosis 	Once daily, 10 mg	28-tab pack of 10 mg tablets	£23.12	£23.12	£301.39
Alendronate	Fosamax Once Weekly	Merck Sharp and Dohme	<ul style="list-style-type: none"> • treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures 	Once weekly, 70 mg	4-tab pack of 70 mg tablets	£22.80	£22.80	£296.40
Alendronate	Generic	-	<ul style="list-style-type: none"> • treatment of osteoporosis in men and post-menopausal women to prevent fractures • treatment of glucocorticoid-induced osteoporosis • prevention of bone loss in post-menopausal women considered at risk of developing osteoporosis 	Once daily, 10 mg	28-tab pack of 10 mg tablets	£8.30	£1.45	£18.90
Alendronate	Generic	-	<ul style="list-style-type: none"> • treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures 	Once weekly, 70 mg	4-tab pack of 70 mg tablets	£4.12	£0.91	£11.83
Alendronate	Generic	-	<ul style="list-style-type: none"> • treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures 	Once weekly, 70 mg	Oral solution in 4x100ml vials with 70 mg	-	£22.80	£296.40
Alendronate with colecalciferol	Fosavance	MSD	<ul style="list-style-type: none"> • treatment of postmenopausal osteoporosis in women at risk of vitamin D insufficiency to reduce the risk of vertebral and hip fractures 	Once-weekly, 70 mg	4-tab pack of 70 mg tablets with colecalciferol	-	£22.80	£296.40
Denosumab	Prolia	Amgen	<ul style="list-style-type: none"> • bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures • treatment of postmenopausal osteoporosis in women with an increased risk of fractures 	Twice a year, 60 mg	60 mg in a 1ml injectable solution	£183	£183	£366
Etidronate	Didronel	Warner Chilcott	<ul style="list-style-type: none"> • discontinued 			£21.12	-	
Raloxifene	Evista	Daiichi Sankyo	<ul style="list-style-type: none"> • treatment and prevention of osteoporosis in postmenopausal women (A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated) 	Once daily, 60 mg	28-tab pack of 60 mg tablets	£17.06	£17.06	£222.39
Raloxifene	Evista	Daiichi Sankyo	<ul style="list-style-type: none"> • treatment and prevention of osteoporosis in postmenopausal women (A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated) 	Once daily, 60 mg	84-tab pack of 60 mg tablets	£59.59	£59.59	£258.93
Risedronate	Actonel	Warner Chilcott	<ul style="list-style-type: none"> • treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures, • treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures 	5 mg, once-daily	28-tab pack of 5 mg tablets	£19.10	£17.99	£234.51

Technology	Brand	Manufacturer	Indication (bold indicates new indication since TA160,161 or 204)	Dose / schedule	Preparation	Original price	Current price	Current Annual price
			<ul style="list-style-type: none"> • prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis • maintaining or increasing bone mass in postmenopausal women undergoing long-term (more than 3 months) systemic corticosteroid treatment at doses greater than 7.5 mg of prednisone (or equivalent) per day 					
Risedronate	Actonel Once a Week	Warner Chilcott	<ul style="list-style-type: none"> • treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures • treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures • treatment of osteoporosis in men at high risk of fractures 	35 mg, once-weekly	4-tab pack of 35 mg tablets	£20.30	£19.12	£248.56
Risedronate	Generic	-	<ul style="list-style-type: none"> • treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures, • treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures • prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis • maintaining or increasing bone mass in postmenopausal women undergoing long-term (more than 3 months) systemic corticosteroid treatment at doses greater than 7.5 mg of prednisone (or equivalent) per day 	5 mg, once-daily	28-tab pack of 5 mg tablets	-	£13.59	£177.16
Risedronate	Generic	-	<ul style="list-style-type: none"> • treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures • treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures • treatment of osteoporosis in men at high risk of fractures 	35 mg, once-weekly	4-tab pack of 35 mg tablets	-	£1.20	£15.60
Risedronate with calcium carbonate and colecalciferol	Actonel Combi	Warner Chilcott	<ul style="list-style-type: none"> • treatment of postmenopausal osteoporosis in women to reduce risk of vertebral or hip fractures 	35 mg, once-weekly	4-tab pack of 35 mg tablets plus Ca+ sachets	-	£19.12	£248.56
Strontium ranelate	Protelos	Servier	<ul style="list-style-type: none"> • treatment of osteoporosis in adult men at increased risk of fracture • treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures 	Once daily, 2 g	28 sachets containing 2 g granules for oral suspension	£25.60	£27.08	£353.01
Teriparatide	Forsteo	Eli Lilly	<ul style="list-style-type: none"> • treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture • reduction of vertebral and non-vertebral fractures (but not hip fractures) in postmenopausal women, • treatment of glucocorticoid-induced osteoporosis in women and men at increased risk for fracture 	20 micrograms Daily	28-day pre-filled pen with 2.4 ml at 250 micrograms per ml	£271.88	£271.88	£3544.15 (max cost x2)

Summary of new evidence and ongoing clinical trials

In TA160 and 161 two suggestions for research were recommended:

- Given the evidence that the benefits of one of the bisphosphonates (alendronate) may continue for several years after the end of treatment, the Committee recommended that research should be carried out to define the optimal duration of treatment with individual bisphosphonates.
- The Committee recommended research into the long-term effects of bisphosphonates on bone quality, given the inhibitory effects on bone resorption of these drugs.

There are no ongoing studies which specifically address these research recommendations.

TA204 had no research recommendations.

Alendronate

According to the manufacturer of proprietary alendronate, there are no plans for an extension to the marketing authorisations for the primary and/or secondary prevention of osteoporotic fragility fractures in postmenopausal women. Furthermore the manufacturer is not aware of any new evidence pertaining to alendronate for these indications.

There is an ongoing clinical trial comparing the effect of ongoing treatment with alendronate or a drug holiday on the fracture risk in osteoporotic patients with bisphosphonate long term therapy (NCT01512446) as well as a randomised clinical trial comparing low dose alendronate (70mg/day) with vitamin D3 compared with placebo for the prevention of osteoporosis in postmenopausal women (NCT00463268). Alendronate in combination with vitamin D3 is also being studied in an ongoing trial with calcitriol in postmenopausal women in China.

Raloxifene

According to the manufacturer, there are no plans to extend the marketing authorisation for raloxifene. The manufacturer is not aware of any new evidence in relation to the appraisal raloxifene for these indications.

Ongoing studies include a comparison of raloxifene and strontium ranelate on compliance and efficacy in women with postmenopausal osteoporosis (NCT01544894) and a post approval safety study in the European Union comparing bazedoxifene with bisphosphonates or raloxifene in postmenopausal women with osteoporosis (NCT01416194).

Risedronate

According to the manufacturer, there are no plans to extend the marketing authorisation for risedronate. The manufacturer is not aware of any new evidence in relation to the appraisal risedronate for these indications.

No ongoing relevant trials were found for risedronate except as an active comparator – see NCT00887354 listed below for teriparatide.

Denosumab

The manufacturer of denosumab does not anticipate any further extensions to the marketing authorisation for denosumab in this patient population. However, denosumab has received a license extension for male osteoporosis and is currently suspended as the manufacturer has informed NICE that they will not provide an evidence submission for the appraisal.

No significant new evidence has become available since the publication of TA204, beyond long term extension data from studies already included in the original submission for TA204. This includes the reporting of results from the open-label, active-treatment extension of the FREEDOM study at years five and six investigating the efficacy and safety of denosumab in women with postmenopausal osteoporosis which showed a maintained reduction in bone turnover and increased BMD, with low fracture rates (Papapoulos, 2011 and Brown 2011 ACR abstract).

The manufacturer also conducted a 24-month, randomised, adherence preference crossover comparison with alendronate in postmenopausal women where participants received alendronate then denosumab or denosumab then alendronate, over successive 12-month periods. After receiving both treatments, women reported greater satisfaction with injectable denosumab and preferred it over oral alendronate (Freemantle 2011).

In a follow-up to the FREEDOM study, fifteen people were enrolled in a cohort study to evaluate the effects of denosumab discontinuation at the tissue level. The results of this study showed normal histology and bone remodelling similar to those observed in untreated postmenopausal women with osteoporosis. This was interpreted to indicate that the effects of denosumab on bone turnover were fully reversible (Brown, 2011 JMBR).

Ongoing studies include a randomised, open-label study evaluating the safety and efficacy of denosumab and monthly risedronate in postmenopausal women transitioned from weekly or daily alendronate therapy (NCT00919711) and a randomised, open-label study evaluating the safety and efficacy of denosumab and ibandronate in postmenopausal women suboptimally treated with daily or weekly bisphosphonates (NCT00936897). There is also a clinical study which has completed, but not reported, on the efficacy and safety of transitioning postmenopausal women on current alendronate to denosumab (NCT00377819).

Also ongoing are several six-month randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy and safety of denosumab in postmenopausal women with osteoporosis from Korea, India and Japan (NCT01457950, NCT01495000, NCT00680953).

Strontium ranelate

Strontium ranelate is currently licensed for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures.

[REDACTED] In April 2013, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended restrictions in the use of strontium ranelate, following the evaluation of data showing an increased risk of heart problems, including heart attacks. The PRAC recommended that the following changes should be implemented to the prescribing information for strontium ranelate until further evaluation and considered by the CHMP:

- Strontium ranelate should only be used for the treatment of severe osteoporosis in postmenopausal women at high risk for fracture and severe osteoporosis in men at increased risk of fracture.
- Strontium ranelate should not be used in patients with current or past history of ischaemic heart disease (such as angina or a heart attack), peripheral arterial disease (obstruction of large blood vessels, often in the legs) or cerebrovascular disease (diseases affecting the blood vessels supplying the brain, such as stroke).
- Strontium ranelate should not be used in patients with hypertension (high blood pressure) that is not adequately controlled by treatment.

On 25 April 2013, the EMA's Committee for Medicinal Products for Human Use (CHMP) confirmed the recommendations made by the PRAC. The CHMP opinion will be sent to the European Commission for a legally binding decision and a further wide-ranging evaluation of the benefits and risks of strontium ranelate will now be conducted by the PRAC and CHMP.

The manufacturer provided information about the results of a large comparative bone biopsy study evaluating the effects of strontium ranelate compared with alendronate on bone formation. After 12 months, a larger statistically significant improvement was observed with strontium ranelate than with alendronate (Chavassieux, 2011).

The manufacturer also provided the details of a randomised, double-blind, 2-year long trial was carried out in 4 countries and involved 88 postmenopausal women with osteoporosis comparing the effects of strontium ranelate to alendronate on bone microarchitecture assessed by high resolution CT scan (Rizzoli, 2012). Over two years, there was a statistically significant improvement bone thickness of participants receiving strontium ranelate where no improvement was seen in those receiving alendronate (Rizzoli, 2012).

The manufacturer also provided results of a trial studying the effects of strontium ranelate in patients previously treated with bisphosphonates. At all time points studied, bone mineral density was significantly greater in the bisphosphonate-naive group (Middleton 2010, 2012).

A small trial studying the effects of strontium ranelate treatment after long-term bisphosphonate treatment. Outcome measures included bone volume, trabecular thickness, and strontium content. Results showed increases in all outcome measures (Busse, 2010).

The manufacturer also provided a summary of the results of a 10 year open-label extension of the SOTI and TROPOS studies (Reginster 2012). This study enrolled

postmenopausal women with osteoporosis who had completed 5 years of treatment with strontium ranelate or placebo, plus a further 5 years of treatment. Bone mineral density was observed to increase significantly throughout treatment.

Teriparatide



The manufacturer also provided results from two observational studies in postmenopausal women with severe osteoporosis comparing the fracture rate, back pain and HRQoL during and after discontinuation of teriparatide. Results showed a reduction in the incidence of fractures (Farhleitner-Pammer, 2011) and a reduction in back pain and improvement in HRQoL (Jakob, 2012).

In another study, the effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures was studied. No differences in back pain-related endpoints were observed, but teriparatide treatment showed greater skeletal benefit than risedronate (Hadji, 2011).

Ongoing studies include two 24-month randomised studies evaluating teriparatide on fracture healing in men and postmenopausal women with a recent femoral neck fracture. Outcome measures include healing on X-rays, number of reoperations, recovery of walking ability, pain control, and quality of life.

Other ongoing trials include a study observing the effect of teriparatide in combination with antiresorptive treatment after 9 months of teriparatide monotherapy (NCT01535027), a study comparing continuous versus cyclic treatment with teriparatide combined with alendronate, another drug for osteoporosis, or teriparatide alone in women with osteoporosis (NCT00668941) and a study comparing the clinical effectiveness of teriparatide after alendronate or risedronate therapy in osteoporotic postmenopausal women (NCT00130403).

Head to head trials include an ongoing trial comparing teriparatide with zoledronic acid in postmenopausal osteoporotic women. Outcome measures include bone biopsy measurements (NCT00927186). Another trial compares teriparatide with risedronate in men and postmenopausal women with low bone mass and a recent hip fracture (NCT00887354).

Appendix 3 – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE’s work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	Yes, however not as a full review of the evidence.
The guidance should be incorporated into an on-going clinical guideline.	<p>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No.

Options	Consequence	Selected – ‘Yes/No’
The guidance should be updated in an on-going clinical guideline.	<p>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.</p> <p>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</p>	No.
The guidance should be transferred to the ‘static guidance list’.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	No.

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

- i. The technology falls within the scope of a clinical guideline (or public health guidance)
- ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement
- iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment
- iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;
 - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
 - There is evidence of unjustified variation across the country in access to a treatment

- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
 - The treatment is excluded from the Payment by Results tariff
- v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 4 Supporting information

Relevant Institute work

Published

The assessment and prevention of falls in older people. Clinical Guideline 21, issued November 2004. Review decision July 2011: to be updated. The update is in progress.

In progress

Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures. Multiple technology appraisal, expected date of issue December 2012.

EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing. Medical Technology, expected date of issue December 2012.

Osteoporosis: assessing the risk of fragility fracture. Clinical guideline, expected date of issue June 2012. The scope for this guideline specifies the following clinical issues that will not be covered:

- a) Drugs to prevent fractures.
- b) Fracture and post-fracture management.

This clinical guideline superseded the planned Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk in 2010.

*In topic selection*¹¹



¹¹ Information held by the NICE Topic Selection Team is treated as being commercially sensitive by default. Details of the topics considered by NICE's Topic Selection programme may be available on the NICE website, providing the manufacturers of the technologies under discussion have consented to the release of this information.

Details of changes to the indications of the technology

Indication considered in original appraisal – TA160 and TA161	Proposed indication (for this appraisal)
<p>Alendronate is an oral bisphosphonate that has a UK marketing authorisation as a once-weekly preparation (70 mg) for the treatment of postmenopausal osteoporosis. It also has a marketing authorisation at a daily dose of 10 mg for the treatment of osteoporosis in postmenopausal women to prevent fractures.</p> <p>Nonproprietary alendronate (Teva UK) costs £4.12 for four 70 mg tablets and £8.30 for twenty-eight 10 mg tablets (excluding VAT; NHS Drug Tariff, 24 February 2008).</p> <p>Proprietary alendronate (Fosamax; Merck Sharp & Dohme) is priced at £22.80 for four 70 mg tablets and £23.12 for twenty-eight 10 mg tablets (excluding VAT; 'British national formulary' [BNF] edition 54).</p> <p>Costs may vary in different settings because of negotiated procurement discounts.</p>	<p>Once weekly (70mg) is indicated for treatment of postmenopausal osteoporosis (Fosamax Once Weekly; Merck Sharp & Dohme) a 4-tab pack has a net price of £22.80.</p> <p>The daily 10mg dose is indicated for treatment of osteoporosis in postmenopausal women and in men. It is also indicated for the treatment of glucocorticoid-induced osteoporosis and prevention of bone loss in postmenopausal women considered at risk of developing the disease.</p> <p>Proprietary alendronate (Fosamax; Merck Sharp & Dohme) remains the same price (eBNF 63. A new formulation of proprietary alendronate with colecalciferol is also (Fosavance; Merck Sharp & Dohme at 70mg for a 4-tab pack at a net price of £22.80.</p> <p>Alendronic acid (Non-proprietary):</p> <p>Tablets, alendronic acid (as sodium alendronate) 10 mg, net price 28-tab pack is £1.44; 70 mg, 4-tab pack is £1.10.</p> <p>Oral solution, sugar-free, alendronic acid (as sodium alendronate) 70 mg/100 mL, net price 4 x 100-mL is £22.80 (eBNF 63).</p>

Indication considered in original appraisal – TA160 and TA161	Proposed indication (for this appraisal)
<p data-bbox="188 311 735 584">Etidronate (Didronel) is an oral bisphosphonate that has a UK marketing authorisation for the treatment of osteoporosis. The drug is administered in 90-day cycles, with each cycle consisting of etidronate (400 mg/day) for 14 days followed by calcium carbonate (1.25 g/day) for the remaining 76 days.</p> <p data-bbox="188 645 678 779">The price per 90-day pack is £21.12 (excluding VAT; BNF 54). Costs may vary in different settings because of negotiated procurement discounts.</p>	<p data-bbox="764 311 1302 546">Treatment of osteoporosis and prevention of bone loss in postmenopausal women considered at risk of developing osteoporosis. Didronel PMO is particularly indicated in patients who are unable or unwilling to take oestrogen replacement therapy.</p> <p data-bbox="764 562 1262 663">Didronel PMO is also indicated for the prevention and treatment of corticosteroid induced osteoporosis.</p> <p data-bbox="764 701 1283 902">Didronel PMO therapy is a long-term cyclical regimen administered in 90-day cycles. Each cycle consists of Didronel 400mg tablets for the first 14 days, followed by Cacit 500mg tablets for the remaining 76 days.</p> <p data-bbox="764 940 1283 1003">The net price per 90 day pack is £19.89 (eBNF 63).</p>

Indication considered in original appraisal – TA160 and TA161	Proposed indication (for this appraisal)
<p>Risedronate (Actonel) is an oral bisphosphonate that has a UK marketing authorisation at a dosage of 5 mg/day or 35 mg/week for the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures, and for the treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.</p> <p>Prices are £19.10 for twenty-eight 5 mg tablets and £20.30 for four 35 mg tablets (excluding VAT; BNF 54). Costs may vary in different settings because of negotiated procurement discounts.</p>	<p>At 5mg/day: Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis.</p> <p>To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses ≥ 7.5mg/day prednisone or equivalent.</p> <p>At 35mg/week: Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip</p> <p>Treatment of osteoporosis in men at high risk of fractures.</p> <p>Proprietary risedronate (Actonel) 5mg net price 28-tab pack is £17.99; 35 mg, net price 4-tab pack is £19.12 (eBNF 63). Risedronate sodium (Non-proprietary) 5 mg, net price 28-tab pack is £17.99; 35 mg, 4-tab pack is £19.12 (eBNF 63).</p>
<p>Raloxifene (Evista) has marketing authorisation for the treatment of osteoporosis in postmenopausal women. The recommended dosage is 60 mg/day.</p> <p>The prices of 28 and 84 tablet packs are £17.06 and £59.59, respectively (excluding VAT; BNF 54). Costs may vary in different settings because of negotiated procurement discounts.</p>	<p>Raloxifene is indicated for the treatment and prevention of osteoporosis in postmenopausal women. The dosage is 60mg/day.</p> <p>The prices remain the same (eBNF 63).</p>

Indication considered in original appraisal – TA160 and TA161	Proposed indication (for this appraisal)
<p>Strontium ranelate has a UK marketing authorisation for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures. The recommended dose is one 2 g sachet taken daily as a suspension in water.</p> <p>The price of a 28-sachet pack is £25.60 (excluding VAT; BNF 54). Costs may vary in different settings because of negotiated procurement discounts.</p>	<p>The indication remains the same.</p> <p>The prices remain the same (eBNF 63).</p>

Indication considered in original appraisal not included in the above table – TA161	Proposed indication (for this appraisal)
<p>Teriparatide has a marketing authorisation in the UK for the treatment of established osteoporosis in postmenopausal women. The recommended dose is 20 micrograms administered once daily by subcutaneous injection in the thigh or abdomen. Patients taking teriparatide must receive training in the injection technique. At the time of appraisal, the maximum total duration of treatment was restricted, by the marketing authorisation, to 18 months (see the summary of product characteristics for current information).</p> <p>The price of a 28-day pre-filled pen is £271.88 (excluding VAT; BNF 54). Costs may vary in different settings because of negotiated procurement discounts.</p>	<p>Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated.</p> <p>Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.</p> <p>The recommended dose is 20 micrograms administered once daily by subcutaneous injection in the thigh or abdomen. Patients must be trained to use the proper injection techniques.</p> <p>The maximum total duration of treatment should be 24 months. The 24-month course should not be repeated over a patient's lifetime.</p> <p>The price remains the same at £271.88 net (eBNF 63).</p>

Drug (manufacturer)	Details (phase of development, expected launch date,)
	[REDACTED]
Denosumab (Amgen)	[REDACTED]
Lasofexifene (Pfizer)	[REDACTED]
Odanacatib (Merck)	[REDACTED]
Strontium malonate (Osteologix)	[REDACTED]
Strontium ranelate (Servier)	[REDACTED]
BA058 (Radius health) [REDACTED]	In phase III trial stage, currently recruiting, estimated study completion date December 2013.

Registered and unpublished trials

Trial name and registration number	Details
Alendronate	

Trial name and registration number	Details
<p>A Study to Evaluate Alendronate Sodium /Vitamin D3 Combination Tablets(FOSAMAX PLUS) Versus Calcitriol in the Treatment of Osteoporosis in Postmenopausal Women in China (MK-0217A-264 AM1)</p> <p>NCT01350934</p>	<p>Phase IV.</p> <p>Status: ongoing but not recruiting.</p> <p>Estimated enrollment: 200.</p> <p>Expected completion date: December 2012.</p>
<p>Efficacy and Safety of Odanacatib in Postmenopausal Women Previously Treated With Alendronate (MK-0822-050)</p> <p>NCT01552122</p>	<p>Phase III.</p> <p>Status: not yet open for recruitment.</p> <p>Estimated enrollment: 1378.</p> <p>Expected completion date: February 2015.</p> <p>(Alendronate and odanacatib are used as the placebo in the respective trial arms. Inclusion criteria include 'currently taking alendronate'.)</p>
<p>Osteoporosis Prevention With Low Dose Alendronate</p> <p>NCT00463268</p>	<p>Phase III.</p> <p>Status: enrolling by invitation.</p> <p>Estimated enrollment: 100.</p> <p>Expected completion date: January 2012.</p>
<p>Comparison of the Effect of an Ongoing Treatment With Alendronate or a Drug Holiday on the Fracture Risk in Osteoporotic Patients With Bisphosphonate Long Term Therapy (BILANZ)</p> <p>NCT01512446</p>	<p>Phase III.</p> <p>Status: currently recruiting.</p> <p>Estimated enrollment: 7000.</p> <p>Expected completion date: March 2015.</p>
<p>Etidronate</p>	<p>No ongoing relevant trials found.</p>
<p>Risedronate</p>	<p>No ongoing relevant trials found except as an active comparator – see NCT00887354 listed below for teriparatide.</p>
<p>Raloxifene</p>	

Trial name and registration number	Details
<p>Cohort Study Of Venous Thromboembolism And Other Clinical Endpoints Among Osteoporotic Women Prescribed Bazedoxifene, Bisphosphonates Or Raloxifene In Europe (Bazedoxifene Post Approval Safety Study (PASS) in the European Union (EU).</p> <p>NCT01416194</p>	<p>Phase IV observational study. Status: Enrolling by invitation. Estimated enrollment: 10750. Expected completion date: August 2015.</p>
Raloxifene; Strontium ranelate	
<p>Comparison of Raloxifene and Strontium Ranelate on Compliance and Efficacy in Women With Postmenopausal Osteoporosis</p> <p>NCT01544894</p>	<p>Phase IV. Status: completed (but no publication traced). Estimated enrollment: 80. Expected completion date: October 2011.</p>
Teriparatide	
<p>A Randomized, Double-blind, Placebo-Controlled, Comparative Multicenter Phase 3 Study to Evaluate the Safety and Efficacy of BA058 for Injection for Prevention of Fracture in Ambulatory Postmenopausal Women With Severe Osteoporosis and at Risk of Fracture (teriparatide is the active comparator; BA058 is human parathyroid hormone-related protein analogue)</p> <p>NCT01343004</p>	<p>Phase III. Status: currently recruiting. Estimated enrollment: 2400. Expected completion date: December 2013. Primary outcome measures: new vertebral fractures when compared to placebo Secondary outcome measures: Bone mineral density when compared to teriparatide; non-vertebral fractures when compared to placebo; number of hypercalcaemic events when compared to teriparatide.</p>
<p>Phase IV Study Teriparatide and Antiresorptive Combination Treatment Subsequent to 9 Months of Teriparatide Monotherapy</p> <p>NCT01535027</p>	<p>Phase IV. Status: ongoing, not recruiting. Estimated enrollment: 125. Expected completion date: December 2013.</p>

Trial name and registration number	Details
Skeletal Histomorphometry in Patients on Teriparatide or Zoledronic Acid Therapy NCT00927186	Phase IV. Status: ongoing, not recruiting. Estimated enrollment: 69. Expected completion date: May 2012.
Comparison of the Effects of Teriparatide With Those of Risedronate on Lumbar Spine BMD (Bone Mineral Density) in Men and Postmenopausal Women With Low Bone Mass and a Recent Pertrochanteric Hip Fracture NCT00887354	Phase IV. Status: currently recruiting. Estimated enrollment: 242. Expected completion date: July 2014.
Denosumab	
Denosumab in Current Users of Bisphosphonates for Glucocorticoid-induced Osteoporosis: a Randomized Controlled Trial NCT01465568	Phase IV. Status: currently recruiting. Estimated enrollment: 40. Expected completion date: February 2014.
An Open Label, Single Arm, Extension Study to Evaluate the Long Term Safety and Sustained Efficacy of Denosumab (AMG162) in the Treatment of Postmenopausal Osteoporosis NCT00523341	Phase III extension study. Status: ongoing, not recruiting (people must have completed the 3 year pivotal study). Estimated enrollment: 5600. Expected completion date: August 2015.
A Six Month Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study With a Six Month Open-Label Extension to Evaluate the Efficacy and Safety of Denosumab in Korean Postmenopausal Women With Osteoporosis NCT01457950	Phase III. Status: currently recruiting. Estimated enrollment: 125. Expected completion date: August 2013.

Trial name and registration number	Details
<p>A Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Compare the Efficacy and Safety of Denosumab Versus Placebo in Males With Low Bone Mineral Density</p> <p>NCT00980174</p>	<p>Phase III.</p> <p>Status: ongoing, not recruiting.</p> <p>Estimated enrollment: 242.</p> <p>Expected completion date: July 2012.</p>
<p>A Six-Month Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Denosumab in Indian Postmenopausal Women With Osteoporosis</p> <p>NCT01495000</p>	<p>Phase III.</p> <p>Status: currently recruiting.</p> <p>Estimated enrollment: 250.</p> <p>Expected completion date: March 2013.</p>
<p>A Randomized, Double-Blind, Placebo-controlled Phase 3 Study Evaluating Efficacy and Safety of Denosumab in Japanese Osteoporotic Subjects With Prevalent Fragility Vertebral Fracture(s)</p> <p>NCT00680953</p>	<p>Phase III.</p> <p>Status: ongoing, not recruiting.</p> <p>Estimated enrollment: 1100.</p> <p>Expected completion date: September 2012.</p>
<p>A Randomized Open-Label Study to Evaluate the Safety and Efficacy of Denosumab and Monthly Actonel® Therapies in Postmenopausal Women Transitioned From Weekly or Daily Alendronate Therapy</p> <p>NCT00919711</p>	<p>Phase III.</p> <p>Status: ongoing, not recruiting.</p> <p>Estimated enrollment: 870.</p> <p>Expected completion date: July 2012.</p>
<p>A Randomized Open-Label Study to Evaluate the Safety and Efficacy of Denosumab and Ibandronate in Postmenopausal Women Sub-Optimally Treated With Daily or Weekly Bisphosphonates</p> <p>NCT00936897</p>	<p>Phase III.</p> <p>Status: ongoing, not recruiting.</p> <p>Estimated enrollment: 800.</p> <p>Expected completion date: September 2011 (no publication traced).</p>

Additional information

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Drug and Therapeutics Bulletin (2012). Denosumab for postmenopausal osteoporosis.

Drug and Therapeutics Bulletin (2010). Management of corticosteroid-induced osteoporosis

RADAR (2010). Denosumab for postmenopausal osteoporosis.

National Osteoporosis Guidance Group (2010). Osteoporosis: clinical guideline for prevention and treatment.

Safety information:

An MHRA safety concern about atypical stress fractures with bisphosphonates highlighted in 2008 / 09 has been superseded in 2011 by the European CHMP which concluded that 'rare atypical fractures of the femur are a class effect of bisphosphonates'.

The MHRA in 2009 issued a drug safety update on bisphosphonates and osteonecrosis of the jaw, advice which is featured in eBNF 63.

In 2011 the FDA issued a statement 'about its ongoing review of data from published studies to assess whether use of oral bisphosphonate drugs is associated with an increased risk of cancer of the oesophagus.' The NeLM report of this says "At the current time, the FDA believes that the benefits of oral bisphosphonate drugs in reducing the risk of serious fractures in people with osteoporosis continue to outweigh their potential risks. The FDA review is ongoing and the FDA has not concluded that taking an oral bisphosphonate drug increases the risk of oesophageal cancer. There are insufficient data to recommend endoscopic screening of asymptomatic patients and the FDA will continue to evaluate all available data supporting the safety and effectiveness of bisphosphonate drugs and will update the public when more information becomes available." In 2010 the MHRA concluded there is insufficient evidence to confirm a link.

In March 2012 the European CHMP concluded its review of strontium ranelate which said that while it is an important treatment option for osteoporosis, it should no longer be recommended for use in immobilised patients or patients with venous thromboembolism. This follows advice from a UKMi service in 2011 about when it is appropriate to prescribe strontium ranelate for patients with either renal impairment or on renal replacement therapy.

In 2010 the MHRA issued advice about 'adverse effects on renal function with zoledronic acid'.

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Fahrleitner-Pammer A (2011) Fracture rate and back pain during and after discontinuation of teriparatide: 36-month data from the European Forsteo Observational Study (EFOS). *Osteoporosis International* 10:2709-19

Hadji P (2011) The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. *Osteoporosis International* Dec 13. [published online].

Jakob F (2012) Effects of teriparatide in postmenopausal women with osteoporosis pre-treated with bisphosphonates: 36-month results from the European Forsteo Observational Study. *European Journal of Endocrinology* 166(1):87-97.

Middleton ET (2010) The effect of prior bisphosphonate therapy on the subsequent BMD and bone turnover response to strontium ranelate. *Journal of Bone and Mineral Research* 25(3): 455-462.

Middleton ET (2012) The effect of prior bisphosphonate therapy on the subsequent therapeutic effects of strontium ranelate over two years. *Osteoporosis International* 23: 295-303.

Reginster IY (2012) Maintenance of antifracture efficacy over 10 years with strontium ranelate in postmenopausal osteoporosis. *Osteoporosis International* 23: 1115-1122.

Rizzoli R (2012) Effects of strontium ranelate and alendronate on bone microstructure in women with osteoporosis. *Osteoporosis International* 23:305-315.

Appendix 5 – Implementation submission

Implementation feedback: review of NICE technology appraisal guidance 160, 161 & 204

NICE Technology Appraisal 160 Osteoporosis – primary prevention

NICE Technology Appraisal 161 Osteoporosis – secondary prevention including strontium ranelate

NICE Technology Appraisal 204 Osteoporotic fractures - denosumab

Implementation input required by 02/04/2012

Please contact Rebecca Braithwaite regarding any queries

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1 Routine healthcare activity data

1.1 ePACT and hospital ePACT

This section presents ePACT data on the net ingredient cost (NIC) and the number of prescription items (volume) of alendronic acid, denosumab, disodium etidronate, raloxifene hydrochloride, risedronate sodium, strontium ranelate, and teriparatide and prescribed in primary care and in hospitals that have been dispensed in the community between February 2007 and January 2012.

Figure 1 Cost and volume of alendronic acid (alendronate) prescribed in primary care, and in hospitals that has been dispensed in the community in England

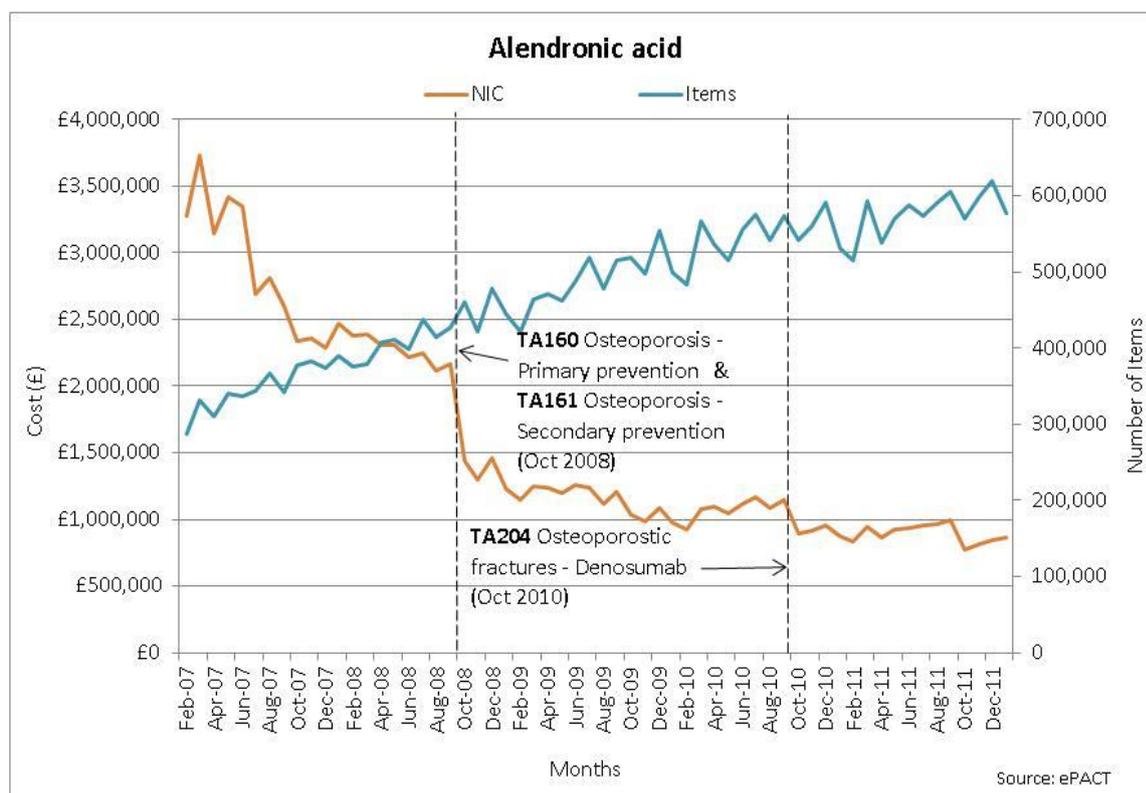


Figure 2 Cost and volume of denosumab prescribed in primary care, and in hospitals that has been dispensed in the community in England

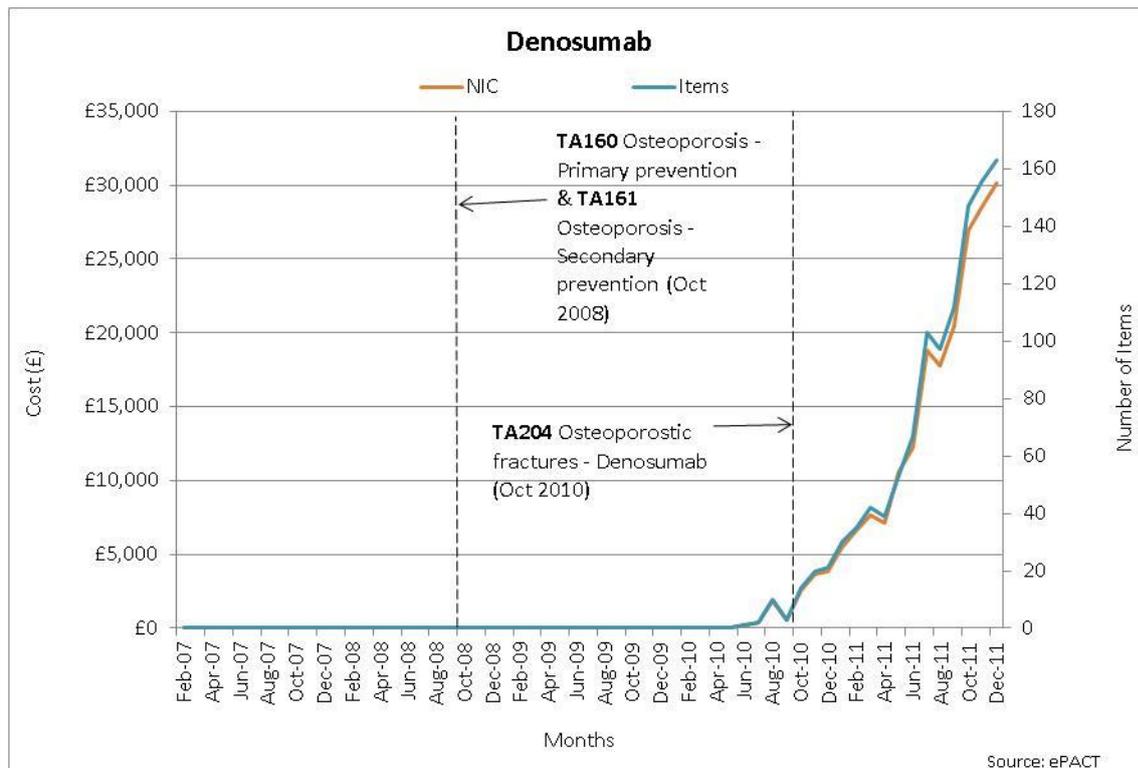


Figure 3 Cost and volume of disodium etidronate prescribed in primary care, and in hospitals that has been dispensed in the community in England

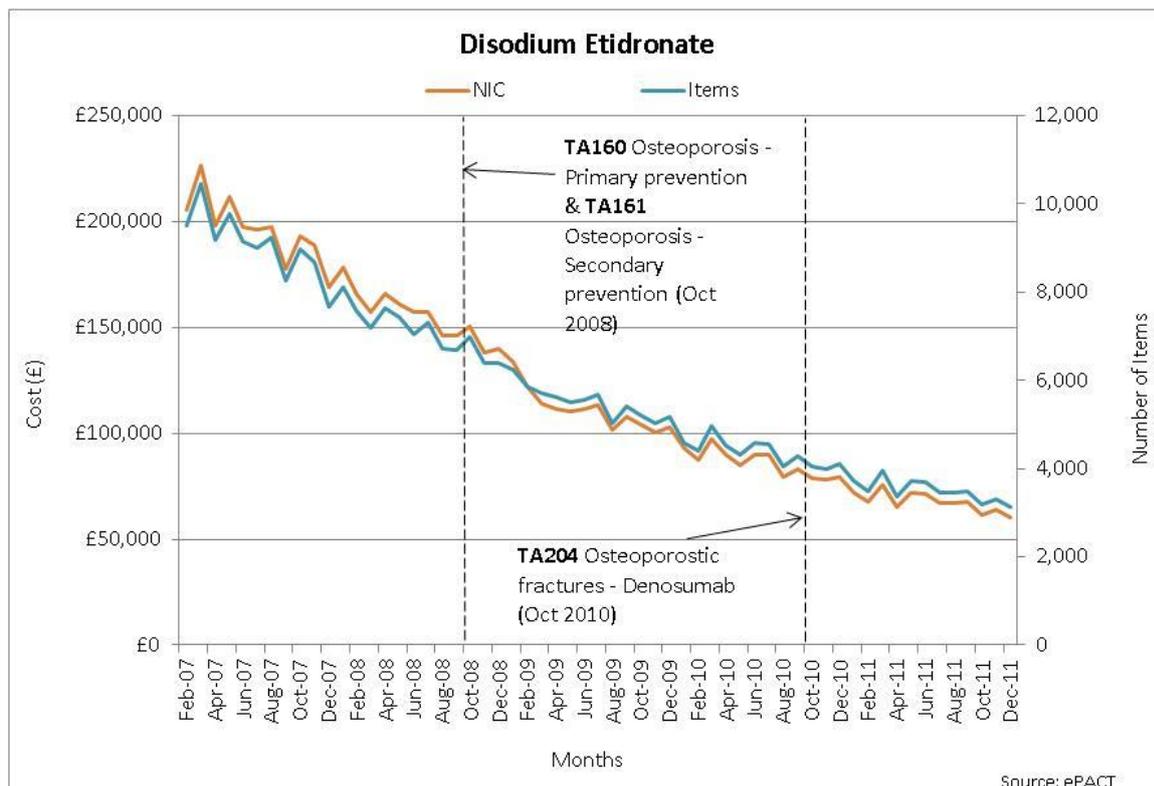


Figure 4 Cost and volume of raloxifene hydrochloride prescribed in primary care, and in hospitals that has been dispensed in the community in England

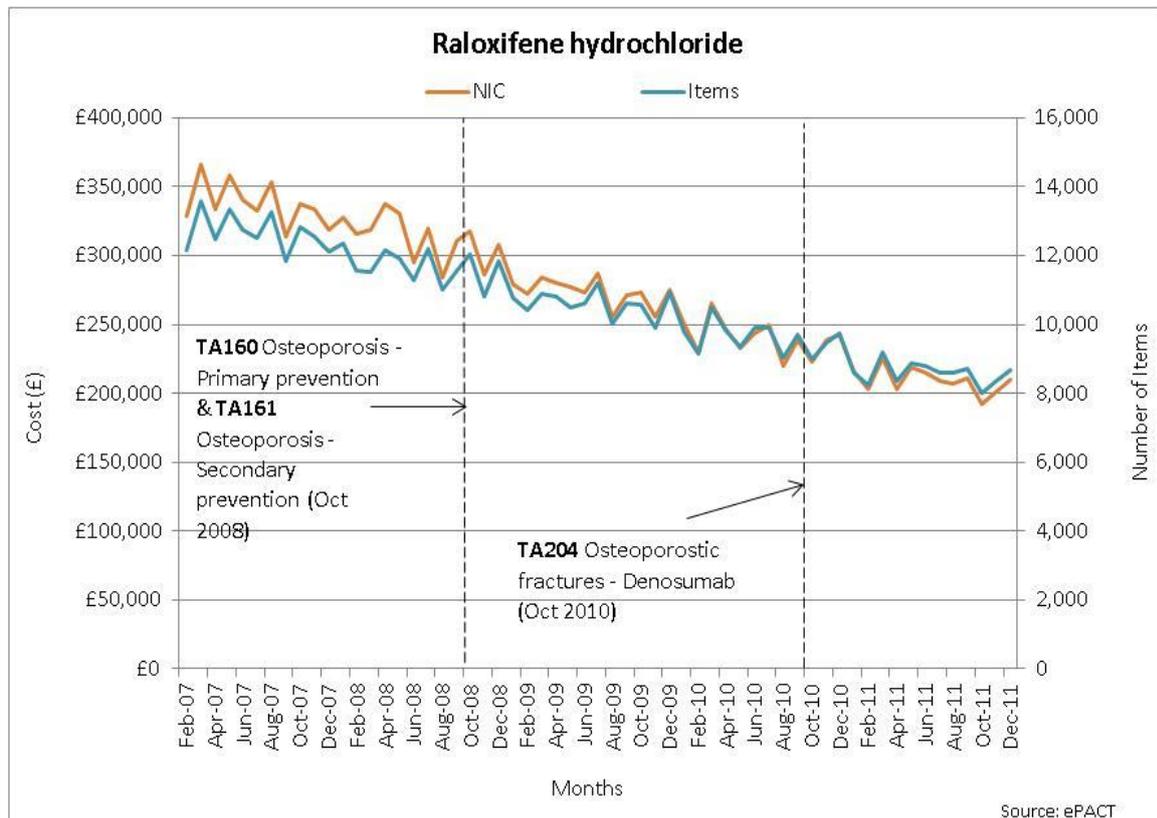


Figure 5 Cost and volume of risedronate sodium prescribed in primary care, and in hospitals that has been dispensed in the community in England

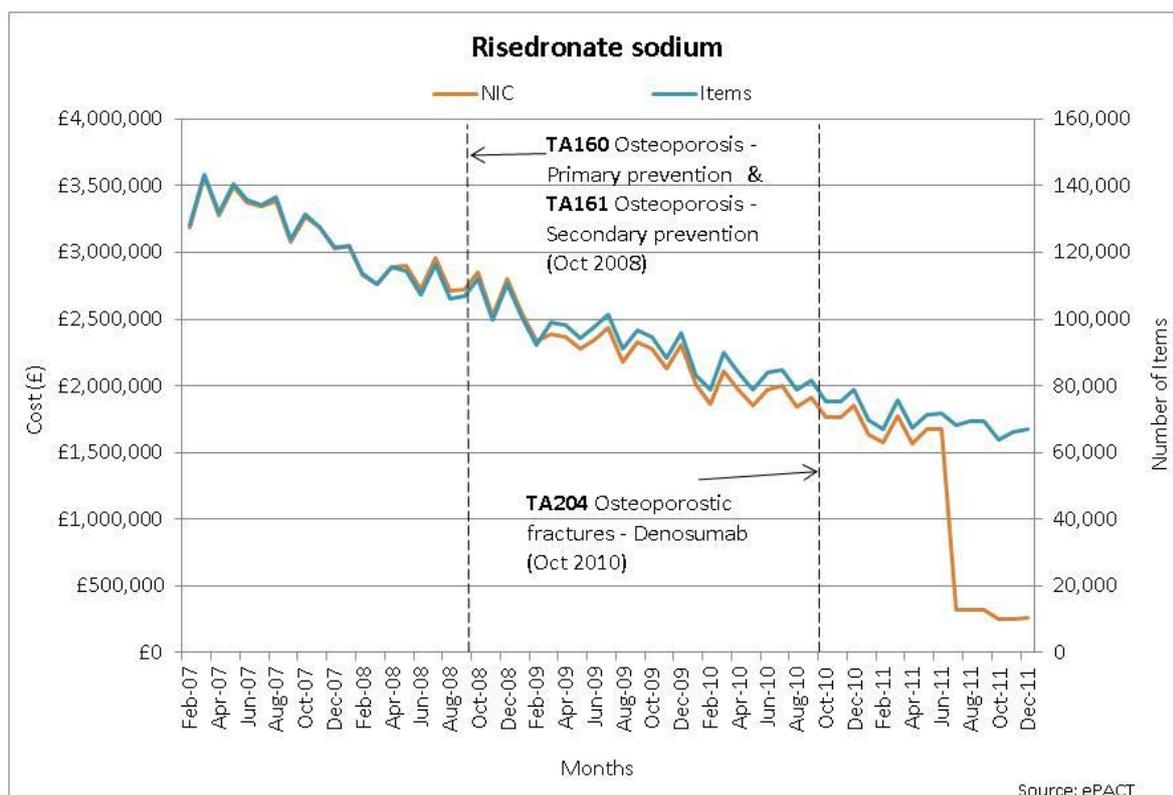


Figure 6 Cost and volume of strontium ranelate prescribed in primary care, and in hospitals that has been dispensed in the community in England

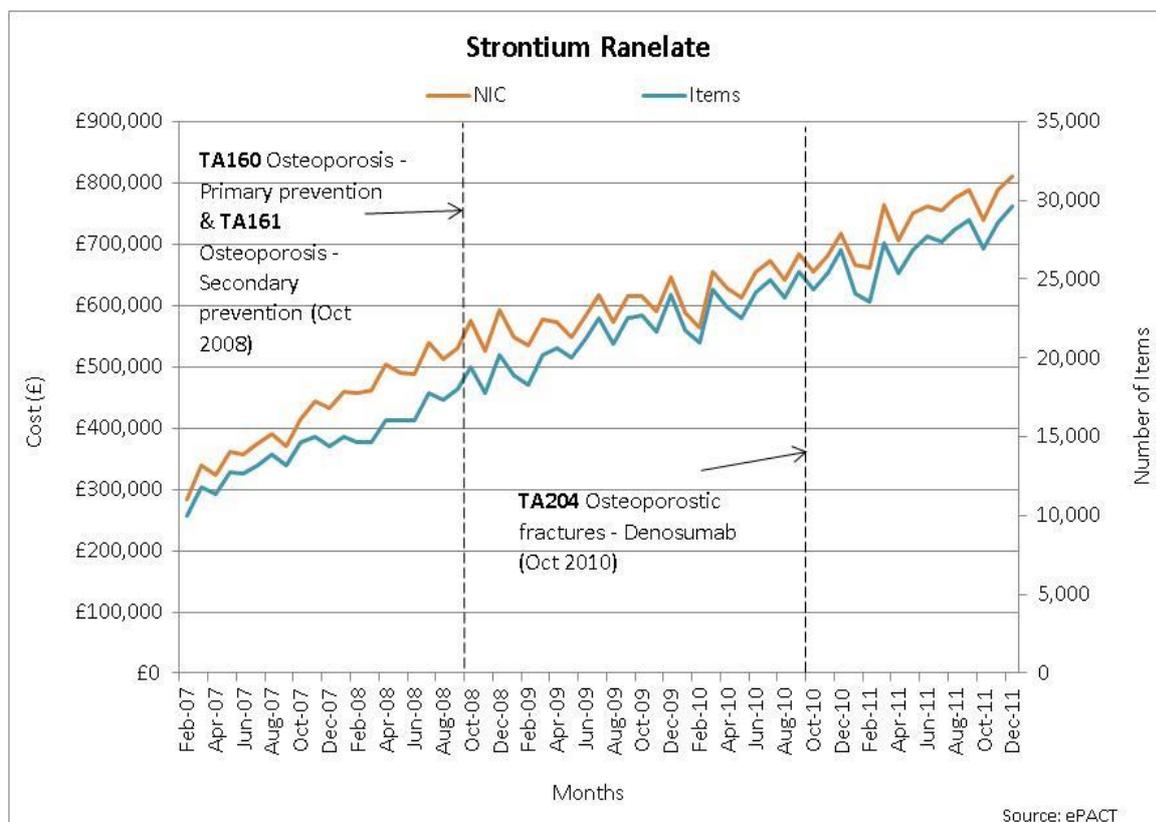
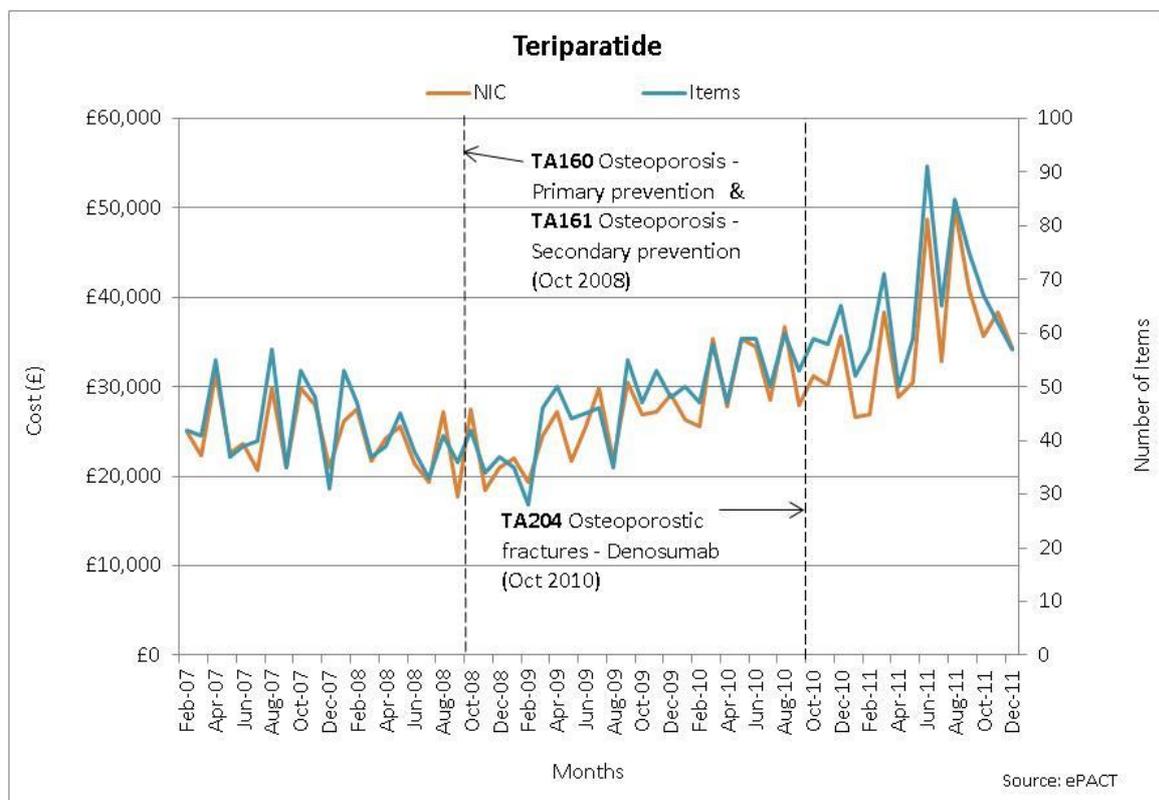


Figure 7 Cost and volume of teriparatide prescribed in primary care, and in hospitals that has been dispensed in the community in England



1.2 Hospital Pharmacy Audit Index (HPAI)

This section presents Hospital Pharmacy Audit Index data on the net ingredient cost (NIC) and volume of alendronic acid, disodium etidronate, raloxifene hydrochloride, denosumab, teriparatide, strontium ranelate, risedronate, and risedronic acid, prescribed and used in hospitals between January 2010 and January 2011.

Table 1 Net ingredient cost of osteoporosis drugs prescribed and used in hospitals between January 2010 and January 2011 in England.

Cost (£)	Jan-10	Apr-10	Jul-10	Oct-10	Jan-11
Alendronic Acid	170309	171047	162465	144946	141674
Etidronic Acid	1555	1067	1008	953	763
Raloxifene	6018	6363	6592	7367	6077
Denosumab	0	0	6132	44092	120683
Teriparatide	719653	679269	690260	709295	717359
Strontium Ranelate	137191	140149	141384	153163	159605
Risedronate	0	0	0	0	0
Risedronic Acid	169815	159856	145582	139958	126824

Table 2 Volume of osteoporosis drugs prescribed and used in hospitals between January 2010 and January 2011 in England.

Volume	Jan-10	Apr-10	Jul-10	Oct-10	Jan-11
Alendronic Acid	60473	59610	58334	59935	57419
Etidronic Acid	80	55	52	49	39
Raloxifene	348	365	379	411	335
Denosumab	0	0	34	241	659
Teriparatide	1034	1056	1052	1155	1130

Strontium Ranelate	5359	5475	5523	5868	5894
Risedronate	0	0	0	0	0
Risedronic Acid	8576	8071	7264	7024	6325

2 Implementation studies from published literature

Information is taken from the uptake database ([ERNIE](#)) website.

2.1 NHS Information Centre for Health and Social Care (2009) [Use of NICE appraised medicines in the NHS in England-Experimental Statistics](#) NHS Information Centre for Health and Social Care

The NICE costing template expected an annual number of 586.1 thousand patients. Assuming that treatment is continuous this would lead to a predicted use of 213,917.0 thousand doses per annum. The observed use in 2008 was 256,691.7 thousand defined daily doses giving a ratio of 1.2 to 1.

2.2 Turk A et al (2010) [Pharmacist independent prescribing - An evaluation of care for patients admitted with fragility fractures](#) *Osteoporosis International* 21 (Suppl 3):S443-S518

Over a 21 month period all patients included in the study were examined by the Pharmacist Independent Prescriber (PIP) for treatments appropriate to secondary prevention of osteoporotic fragility fractures (FF). The PIP assessed 133 inpatients admitted following a fall; three had not suffered a FF but were assessed for primary prevention of osteoporosis as per NICE guidance. The remaining 130 patients had sustained a total of 149 FFs. 8% were referred for DXA scan following NICE guidance.

2.3 Johnston, T et al (2010) [Naughty or 'Nice': Has NICE TA160 changed our prescribing practice?](#) *Osteoporosis International* 21 (suppl 3): S443-S518

The authors compared prescribing against NICE 'eligibility' for primary prevention of osteoporosis in two groups of patients treated for this indication in the period April to

2007-Feb 2009 and subsequent to Feb 2009 to Feb 2010 NICE guidance. Results found that for risedronate/etidronate, 25.0% of prescribing in the pre-cohort conformed, increasing to 33.3% in the post-NICE cohort.

2.4 The NHS Information Centre for Health and Social Care (2011) [Use of NICE-appraised medicines in the NHS in England-2009, Experimental Statistics](#)

This is the second report commissioned by the Metrics Working Group to look at the variation in use of positively appraised medicines in relation to the expected use as predicted by NICE. In all, 47 medicines in 18 groups, relating to 29 technology appraisals were considered. Out of the 12 groups where a comparison could be made (these are presented in Section 1 of the technology section results), observed use by the NHS in England was higher than the predicted use for eight and lower for three.

2.5 Richards, M (2010) [Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE](#)

This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

2.6 Royal College of Physicians (2011) [Falling standards, broken promises Report of the national audit of falls and bone health in older people 2010](#)

The 2010 Audit represents the completion of a five-year audit cycle with a combined organisational and clinical audit. Results found that only 67/171 commissioning organisations reported a mechanism to assess compliance with the NICE TA161. Many clinical services were not adhering to NICE CG21 and TA87 guideline-based treatments to prevent falls and fractures. For example patients with first fractures

were not flagged and many of the exercise programmes being provided were not evidence based.

3 Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

One person commented that NICE TA161 was fantastically useful.

Appendix 1: Healthcare activity data definitions

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions written in hospitals but dispensed in the community (FP10 [HP]) are not included in PACT data. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis.

Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.

IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI)

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies: to wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.