NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (NICE technology appraisal guidance 160)

Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (NICE technology appraisal guidance 161)

This overview is written by members of the team of technical analysts at NICE. It forms part of the information received by the Appraisal Committee and serves as a summary of the evidence and views submitted by consultees and commentators and the Decision Support Unit (DSU) relating to the economic model for NICE technology appraisal guidance 160 and 161. Key issues for discussion at the Appraisal Committee meeting are highlighted. NICE prepared this overview before it received consultees' and commentators' comments on the DSU report. These comments are therefore not addressed in the overview.

The sources of evidence used in the preparation of this document are given in appendix A.

1. Purpose of this overview

The purpose of this overview is to assist the Appraisal Committee in addressing the requirements of the High Court ruling on NICE technology appraisal guidance 160 (primary prevention of osteoporotic fractures) and 161 (secondary prevention, that is, in women who have already sustained a

fracture). The ruling requires that consultees should have the opportunity to comment on an executable version of the Assessment Group economic model.

This document should be read in conjunction with individual comments from consultees and commentators on the executable model, the DSU report and comments on the DSU report.

2. Background

2.1 History

NICE technology appraisal guidance 160 (TA160) and NICE technology appraisal guidance 161 (TA161) were published in October 2008. TA160 recommended alendronate as first-line treatment for the primary prevention of fragility fractures in postmenopausal women with osteoporosis who have specific levels of fracture risk as defined by their age, BMD, and number of independent clinical risk factors for fracture or indicators of low BMD. TA161 recommended alendronate as first-line treatment for the secondary prevention of fragility fractures in post-menopausal women with confirmed osteoporosis. The other drugs (including strontium ranelate) included in the appraisals were recommended for women who cannot take alendronate, at the ages, BMD levels and number of independent clinical risk factors for fracture at which their use becomes cost effective.

A complete list of guidance recommendations from TA160 and TA161 are included in the Committee papers.

The Committee made these decisions after more than ten meetings and were informed by multiple consultee inputs, expert advice, Guideline Development Group discussion and assessment reports produced by School of Health and Related Research, University of Sheffield. The Assessment Group reported analyses from an economic model which included third party confidential information on the relationship between clinical risk factors and fracture risk developed under the auspices of the WHO.

Servier, the manufacturer of strontium ranelate applied for judicial review of the guidance, which was heard in January 2009. Servier argued on three grounds: that NICE had discriminated against disabled people; that a specific clinical trial had not been dealt with properly; and that the appraisal was unfair because NICE could not give its stakeholders, including Servier, access to the Assessment Group economic model, because it contained third-party confidential information. The High Court ruled in favour of NICE on the two grounds of discrimination and handling of clinical data.

On the third ground the judge agreed that NICE was correct in not releasing third-party confidential information but considered that it could have done more to arrange for that information to be made available.

In April 2009, agreement for release of the Assessment Group executable economic model, inclusive of confidential information, was reached with the owner of the confidential information. It was stipulated that the information could be released only for the purposes of commenting on the model and only to consultees who agreed to comply fully with additional confidentiality undertakings. NICE communicated an 'offer to consult' on the model to consultees and commentators.

In May 2009, consultation began on the Assessment Group executable economic model used for TA160 and TA161. Comments received on the model were considered by the Decision Support Unit (DSU) and a DSU report was issued to consultees and commentators for consultation in August 2009.

Details of appraisal history are presented in appendix B.

2.2 The condition

Osteoporosis is a progressive, systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue. Osteoporosis increases the risk of fracture. The risk of fracture is also increased by other clinical factors, for example prior fracture or parental history of osteoporotic fracture.

Diagnosis of osteoporosis is based on the measurement of bone mineral density (BMD) expressed as the T-score, which is the number of standard deviations (SD) below the mean BMD of young adults at their peak bone mass:

- normal BMD: T-score of –1 SD or above
- osteopenia: T-score of between –1 and –2.5 SD
- osteoporosis: T-score of –2.5 SD or below
- established (severe) osteoporosis: T-score of –2.5 SD or below with one or more associated fractures.

2.3 Current management

The aim of interventions for postmenopausal osteoporosis is to prevent further bone loss and to reduce the risk of fractures. Interventions include lifestyle modifications (such as weight-bearing exercise and adequate dietary calcium and vitamin D intake), fall-prevention programmes and drug therapy.

3. The technologies

Information on the drugs included in these appraisals, including acquisition costs at the time of each appraisal, is shown in Table 1.

Table 1 Summary description of technologies

Non-proprietary name	**Proprietary name**	**Manufacturer**	**Dose**	**Acquisition cost excluding VAT** (£/year; as considered for TA160 and TA161)
Alendronate	Fosamax	Merck Sharp & Dohme	Prevention: 5 mg/day Treatment: 10 mg/day or 70 mg once a week	 301.39 296.40
Alendronate	N/A	Teva UK	Treatment: 10 mg/day or 70 mg once a week	 108.20[a] 53.56[a]
Risedronate	Actonel	Procter & Gamble/ Aventis	Prevention and treatment: 5 mg/day Treatment: 35 mg once a week	 248.98 264.63
Etidronate	Didronel PMO	Procter & Gamble	400 mg/day for 14 days of a 90-day cycle followed by calcium carbonate for the remaining 76 days	85.65
Raloxifene	Evista	Eli Lilly	60 mg/day	222.39[b] 258.93[b]
Strontium ranelate	Protelos	Servier	2 g/day	333.71
Teriparatide	Forsteo	Eli Lilly	20 µg/day	3544.15[c]

[a] NHS Drug Tariff, 24 February 2008.

[b] Based on cost of packs of 28 and 84 tablets, respectively.

[c] At the time of the appraisal, marketing authorisation limited duration of treatment with teriparatide to a maximum of 18 months.

4. The evidence

4.1 Clinical effectiveness

Clinical effectiveness evidence considered by the Committee is summarised in the overview presented to the Appraisal Committee in September 2006 ('Technologies for the prevention of osteoporotic fragility fractures in postmenopausal women').

4.1.1 Efficacy

The efficacy values used in the appraisals are given in table 2.

Table 2 Summary of efficacy of technologies: relative risk of fracture, compared with no treatment

Drug	Vertebral fracture	Hip, pelvis and other femoral fractures	Non-vertebral fracture (proximal humerus, rib, sternum, scapula, tibia and fibula fractures)
Alendronate[a]	0.56 (0.46 to 0.68)	0.62 (0.40 to 0.98)	0.81 (0.68 to 0.97)
Trials/participants	*4/7039*	*3/7453*	*6/9973*
Risedronate[a]	0.61 (0.50 to 0.75)	0.74 (0.59 to 0.93)	0.76 (0.64 to 0.91)
Trials/participants	*3/2301*	*3/11770*	*5/12399*
Meta-analysed alendronate and risedronate	0.58 (0.51 to 0.67)	0.71 (0.58 to 0.87)	0.78 (0.69 to 0.88)
Trials/participants	*7/9340*	*6/19233*	*11/22372*
Etidronate[a]	0.40 (0.20 to 0.83)	0.50 (0.05 to 5.34)	1.04 (0.64 to 1.69)
Trials/participants	*3/341*	*2/180* *Assumed no effect in model*	*4/410* *Assumed no effect in model*
Raloxifene[a]	0.65 (0.53 to 0.79)	1.13 (0.66 to 1.96)	0.92 (0.79 to 1.07)
Trials/participants	*1/4551*	*2/6971* *Assumed no effect in model*	*1/6828* *Assumed no effect in model*
Teriparatide[b]	0.35 (0.22 to 0.55)	0.50 (0.09 to 2.73)	0.65 (0.43 to 0.98)
Trials/participants	*1/1326*	*1/1637* *Assumed no effect in model*	*1/1637*
Strontium ranelate[c]	0.60 (0.53 to 0.69)	0.85 (0.61 to 1.19)	0.84 (0.73 to 0.97)
Trials/participants	*2/6551*	*1/4932*	*2/6551*

Data are from the Assessment Group's systematic reviews and meta-analyses unless otherwise indicated.

Figures in brackets are 95% confidence intervals.

[a] Data taken from DSU report (March 2005), appendix 3.

[b] Data taken from assessment report (2003)

[c] Data taken from the strontium ranelate assessment report (2005). Hip fracture data taken from the manufacturer's submission. Relative risk of 0.85, though not statistically significant was used in the model.

Evidence put forward by consultees and commentators on potential increased fracture risk linked to acid-suppressive medication was critiqued by the DSU and presented in the February 2008 DSU critique.[1]

4.2 Cost effectiveness

4.2.1 Submitted evidence

Evidence submitted by consultees and commentators is summarised in the September 2006 overview.[2]

4.2.2 Assessment Group economic evaluation

The Assessment Group cost–utility economic model is described in detail in the 2005 strontium ranelate assessment report. Absolute fracture risks were calculated based on epidemiological data linking a number of independent clinical risk factors with fracture risk, prepared under the auspices of the World Health Organization (WHO) and provided for these appraisals under an academic-in-confidence agreement. These fracture risks were entered into model. The model applied reductions in relative risk for fracture taken from the Assessment Group meta-analysis. Following advice from the Guideline Development Group for the clinical guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' (see www.NICE.org.uk[3]), it was assumed a single estimate of efficacy was used for alendronate and risedronate based on pooled data for these two drugs, and that relative risk remained constant across all ages, T-scores and fracture status.

Within the modelling a stepped net-benefit approach was used to estimate the cost effectiveness of assessment of fracture risk, dual-energy X-ray absorptiometry (DXA) scanning and treatment of women.

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[1] Lloyd Jones M (2008) *Critique of evidence put forward by Servier suggesting an association between acid-suppressive medication and fracture risk.* Sheffield: ScHARR. Available from www.nice.org.uk/nicemedia/pdf/OsteoporosisPrimaryMar08DSUcritique.pdf

[2] September 2006 overview: Technologies for the prevention of osteoporotic fragility fractures in postmenopausal women. London: NICE. Available from www.nice.org.uk/nicemedia/pdf/word/osteo_overview_prim06.pdf

[3] Further information available from guidance.nice.org.uk/CG/Wave7/32

1. ICERs for treatment compared with no treatment were calculated for each intervention for various combinations of age, T-score and number of independent clinical risk factors for fracture and the net benefit of treatment per woman was calculated.

2. The net benefit per woman was multiplied by the number of women in the population estimated to fall within each combination of age, T-score and number of independent clinical risk factors for fracture (based on data used to develop the WHO algorithm). The cost of DXA scanning all of the women in each group was subtracted from the net benefit of treatment for that group, thus providing the net benefit of treatment and DXA scanning for the group.

The model permitted various scenarios s for women with no prior fracture (primary prevention) and for women with prior fracture (secondary prevention) to be considered.

The scenarios considered most plausible by the Appraisal Committee in the development of TA160 and TA161 are detailed in the November 2006 Report[4] and the most recent results are provided in the February 2008 DSU Report[5] (and its May 2008 addendum[6]). For the modelling of primary prevention, a maximum acceptable amount to pay for an additional QALY of £20,000 was applied. For the modelling of secondary prevention, a maximum acceptable amount to pay for an additional QALY of £30,000 was applied. The stepped approach is described in more detail in the September 2006 overview.

[4] Stevenson M (2006). Analyses of cost-effective BMD scanning and treatment strategies for generic alendronate, risedronate, strontium ranelate, raloxifene and teriparatide following corrections to the methodology associated with lower efficacy in some risk factors. Sheffield: ScHARR. Available from www.nice.org.uk/nicemedia/pdf/OsteoAddAnalyses.pdf

[5] Stevenson M (2008). Analyses of cost-effective BMD scanning and treatment strategies for generic alendronate, and the cost-effectiveness of risedronate and strontium ranelate in those people who would be treated with generic alendronate. Sheffield: ScHARR. Available from www.nice.org.uk/nicemedia/pdf/OsteoporosisPrimaryMar08DSUreport.pdf

[6] NICE (2008). Addendum [to Assessment Group economic evaluation]. London: NICE. Available from www.nice.org.uk/nicemedia/pdf/OsteoporosisPrimaryPreventionAddendumFADJul08.pdf

The Committee considered the results of economic analyses in the form of identification and treatment strategies (based on age, T-score and number of independent clinical risk factors for fracture) that resulted in an incremental cost-effectiveness ratio (ICER) within the maximum acceptable amount to pay for an additional QALY, as previously specified, for primary prevention (section 4.3.15 of TA160), and secondary prevention (section 4.3.16 of TA161).

The following assumptions were included in the analysis:

- persistence at 5 years set to 50%
- the efficacy of bisphosphonates on fracture risks associated with factors other than age, BMD and prior fracture status (informed by the epidemiological data, but not proven in clinical trials) set to 50% of that observed for the total population in the trials (with a consequent upward adjustment of the relative risk associated with age, BMD and prior fracture)
- costs set to health resource group values including home-help costs;
- utility multiplier associated with vertebral fracture set to 0.792 in the first year of fracture and 0.909 in subsequent years (as for hip fracture)
- costs of bisphosphonate-related gastrointestinal symptoms are incurred over 5 years
- utility multiplier associated with bisphosphonate-related gastrointestinal symptoms set to 0.91 (included utility losses for non-compliant patients).

In addition to the assumptions above, scenarios were considered where bisphosphonate-related side effects were varied or other drugs were used as second-line treatment options where alendronate could not be taken. The results of a sensitivity analysis which assumed a proven link between acid-suppressant medication and increased fracture rates were also presented for

alendronate and risedronate (no effect of acid-suppressant medication was considered for strontium ranelate).

Assumptions for the Assessment Group's economic analyses for TA160 and TA161, which were considered by the Appraisal Committee, are summarised in table 3. Further details are provided in the February 2008 report and its May 2008 addendum.

Table 3 Summary of assumptions considered in economic analyses for TA160 (primary prevention) and TA161 (secondary prevention)

Drug	**First-line use**	**Second-line use**, that is, for a population for whom use of alendronate first line would be cost effective, but who cannot take alendronate
Alendronate	Alendronate £53.56 per year Identification cost included in analysis of primary prevention. Impact of not including identification cost considered in analysis of secondary prevention. 24% of women in the first treatment month and 3.5% of women thereafter experience bisphosphonate-related side effects	N/A
Alendronate	Alendronate £108.20 per year Identification cost included 24% of women in the first treatment month and 3.5% of women thereafter experience bisphosphonate-related side effects	N/A
Risedronate	Identification cost included in analysis of primary prevention. 2.35% of women in the first treatment month and 0.35% thereafter experienced side effects in analysis primary prevention. Sensitivity analysis considered the impact of assuming 24% of women in the first treatment month and 3.5% of women thereafter experience bisphosphonate-related side effects.	No identification costs 2.35% of women in the first treatment month and 0.35% thereafter experienced bisphosphonate-related side effects
Etidronate	No re-analysis	No re-analysis
Raloxifene	Identification cost included as for risedronate	No identification costs as for risedronate
Strontium ranelate	Identification cost included as for risedronate	No identification costs as for risedronate
Teriparatide	Identification cost included as for risedronate	No identification costs

5. Consultation on the economic model

5.1 Negotiation of release of confidential information and additional undertaking

5.1.1 Servier appeal 2008

NICE considered an appeal from Servier in September 2008, which claimed amongst other points, that NICE had failed to adequately detail the economic analysis undertaken to examine the implications of the use of acid-suppressive medication in patients taking bisphosphonates (alendronate, etidronate or risedronate). This point and other appeal points were dismissed.

The Appeal Panel noted that Servier was also challenging non-release of the Assessment Group economic model in a judicial review application, and that those proceedings would consider the matter further.

At the time of the appeal to NICE in 2008, the judgement of the Court of Appeal relating to 'Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease' (NICE technology appraisal guidance 111 [TA111]) was under appeal to the House of Lords. At the hearing for Servier's appeal against the osteoporosis final appraisal determinations (FADs), the Appeal Panel concluded that until the TA111 appeal to the House of Lords was complete, further release of analysis from other appraisals was not required.

Post appeal actions

Noting the challenges raised in the appeal hearing and the ongoing legal proceedings relating to TA160, TA161 and TA111, NICE attempted further negotiation with the data owner for release of the confidential data within the Assessment Group model.

NICE was advised by the data owner that the data were to be considered as academic in confidence. It noted the algorithms were not published. It

therefore continued to manage the data as confidential and, as a consequence, the economic model containing the confidential information could not be released.

5.1.2 Judicial review 2009

Following the judicial review for TA160 and TA161 in January 2009, the High Court requested that NICE continue negotiating permission to release the Assessment Group executable economic model containing the confidential information. In April 2009, NICE reached agreement with the owner of the confidential information on the release of the economic model for consultation. This agreement was conditional on consultees and commentators agreeing to an undertaking with the owner of the confidential data in addition to the standard confidentiality agreement and undertaking required by NICE.

Eight consultees requested the model and returned the necessary confidentiality undertakings. These parties received a CD-ROM containing the executable version of the economic model which included the confidential information, a document with instructions for running the model and a pro-forma for commenting on the model.

6 Comments on the model

Six responses were received from consultees during the consultation period on the Assessment Group executable economic model. Two of these consultees did not provide comments on the model. Comments on the model were received from:

- Servier
- Bone Research Society (BRS)
- National Osteoporosis Society (NOS)
- Society for Endocrinology

All issues raised in the comments received from the consultees and commentators on the Assessment Group executable economic model are listed in appendix C.

6.1 DSU review of consultee comments

The DSU was commissioned to review comments from consultees on the Assessment Group executable economic model and report to the Appraisal Committee.

- The DSU responded in detail to comments only if they related to the economic model.
- The DSU was of the opinion that many of the comments from consultees and commentators did not relate to the executable economic model but to the appropriateness of specific parameter values that were previously considered by the Appraisal Committee for these appraisals. The DSU did not respond in detail to these comments.

6.1.1 Summary of comments considered relevant to the model

This section should be read in conjunction with the August 2009 DSU report.

The DSU considered that the following issues were relevant to the economic model (see August 2009 DSU report, section 3.1, pages 8–15). Some comments were grouped under common themes, as follows:

Accessibility and transparency

- Inadequate documentation of the model (Servier issue 1, BRS issue 6, NOS issue 1, Society for Endocrinology issue 1)
- Inability to assess the validity of the model, leading to claims that the model is not fully executable (Servier issue 1)

- Inability to directly assess the integrity of the application of the WHO algorithm in the model (Servier issue 2, NOS issue 6)

- Inability to change certain variables in the model (Servier issue 1, NOS issue 6)

Modelling approaches

- Disagreement with certain modelling approaches:

    - fixed BMI (Servier issue 3, BRS issue 4, NOS issue 6),

    - weight applied to risk factors (Servier issue 5) and

    - rationale for choice of clinical risk factors considered (Servier issue 4, BRS issues 7 and 8, NOS issues 4 and 5).

- Amalgamation of clinical risk factors may lead to inaccuracy in the estimates of cost effectiveness (Servier issue 13, BRS issue 3).

- Uncertainty around methodology used to extend the 10-year time horizon (Servier issue 6, NOS issue 6).

Model inputs

- Appropriateness of population data used (BRS issue 2, NOS issue 2).

- Disagreement with the annual risk associated with clinical risk factors (Servier issues 2 and 7).

- Omission of certain clinical risk factor interactions (Servier issue 2, BRS issues 5 and 9) including omission of mortality risks associated with clinical risk factors (Servier issue 2).

6.1.2 Summary of comments considered not relevant to the model

The DSU considered that the following comments received were not related to the functioning of the economic model, but to issues and assumptions that

had already been documented and were available to consultees and commentators to comment upon earlier in the development of the appraisal. In addition the Appraisal Committee had made judgements about these issues and assumptions previously (see August 2009 DSU report, section 3.2, pages 15–17). It was not for the DSU to comment on the Appraisal Committee's judgement.

These included comments on the following and have been referred to previously as follows:

Discount rate (Servier issue 8)

Discount rates used were described in the 2005 Strontium Ranelate Assessment Report and in the FADs for TA160 (section 4.2.9) and TA161 (section 4.2.10), as follows: "Discount rates of 6% per year for costs and 1.5% per year for health benefits were applied, in accordance with NICE methods relevant to this appraisal". Furthermore, FAD sections 4.3.16 of TA160 and 4.3.17 of TA161 state: "The Committee noted that current discount rates used by the Treasury, the Department of Health and NICE result in a cost-effectiveness calculation less favourable to the drugs than the discount rates used in the analysis considered by the Committee".

Compliance (Servier issue 9)

Lack of compliance was modelled in sensitivity analyses assuming that the patient incurs 1 month of drug costs but received no health benefits, as described in the 2005 strontium ranelate assessment report (pages 57, 106). These results were understood by the Appraisal Committee at the time of the appraisal. Section 4.2.10 of TA160 states: "For the base case, the model assumed 50% persistence with treatment. In addition to the base case, the Assessment Group undertook a number of sensitivity analyses using alternative assumptions including: persistence with treatment (25% or 75% at 5 years)."

Costs associated with fracture (Servier issue 11)

Initially, as stated in the 2005 Strontium Ranelate Assessment Report that were obtained from a systematic review by Kanis et al inflated to 2003/2004 values. Following consultation, costs were set to health resource group values including home-help costs available at the time of the appraisal (TA161 section 4.2.17), in accordance with NICE methods.

Strategy for identification of women at high risk (Servier Issue 13)

The pathway for the identification of women at high risk is documented in the 2005 strontium ranelate assessment report (pages 98–100) which was available to consultees and commentators at the time of the appraisal. Furthermore, the way in which the identification of women at high risk was included within the model was understood and agreed by the Committee, as noted in the section 4.3.8 of TA160 and 4.3.10 of TA161:

"The Committee acknowledged the efforts of the Assessment Group to build on the model used previously, particularly in using epidemiological data and a fracture risk algorithm developed under the auspices of the WHO to calculate transition probabilities and to model the identification approaches"

Utility values used for vertebral fracture (Servier Issue 12)

The utility values assumed for vertebral fracture were agreed upon by the Committee, as stated below:

- "[The]…utility multiplier associated with vertebral fracture set to 0.792 in the first year of fracture and 0.909 in subsequent years (as for hip fracture)" (section 4.2.16 of TA160 and 4.2.17 of TA161).

- "The Committee considered the utility multiplier used in the base-case analysis for the first year after a vertebral fracture and noted that it was based on a hospitalised patient group and not on a typical group of patients with vertebral fractures. Consequently it was considerably lower than the utility value modelled for a hip fracture. Although the

Committee acknowledged that vertebral fracture can lead to greatly reduced quality of life, it considered that its true value would not greatly outweigh the utility decrement associated with a hip fracture. Therefore, the Committee considered it reasonable to assume that the disutility in the first year after a vertebral fracture was equivalent to the disutility in the first year after a hip fracture and decided to include this assumption in the base-case analysis" (section 4.3.12 of TA160 and 4.3.13 of TA161).

Disutility applied for side effects, which was the same for strontium ranelate and bisphosphonates (Servier issue 10)

Strontium ranelate is not associated with the same adverse gastrointestinal effects as bisphosphonates, however, the clinical data for strontium ranelate indicate other adverse effects, specifically venous thromboembolism. As this adverse effect was not formally included in the model, the Committee agreed to set the base case assumptions for strontium ranelate to the same as for bisphosphonates.

This is described in section 4.2.9 of TA160 and 4.2.10 of TA161 as follows: "It was assumed that women who experience bisphosphonate-related side effects had 91% of the utility of women who do not have such side effects. In base-case analyses for all of the drugs under consideration this was applied to 2.35% of women in the first treatment month and 0.35% of women thereafter and, in sensitivity analyses for bisphosphonates, to 24% of women in the first treatment month and 3.5% of women thereafter. In the case of strontium ranelate, the effect on VTE was not included in the model".

Sensitivity analysis on disutility (Servier issue 10, BRS issue 1, NOS issue 3)

Section 4.3.14 of TA160 (and equivalent section 4.3.15 of TA161) describes the Committees conclusions about the assumptions on side effects as follows: "The Committee considered the assumptions used in the modelling

for the side effects of bisphosphonates, in which women who experience bisphosphonate-related side effects had 91% of the utility of women who did not have such side effects. In the base case, this was applied to 2.35% of patients in the first treatment month and 0.35% of patients thereafter. Taking into account the persistence data (sections 4.1.31 and 4.1.32) and the comments received from consultees and commentators that about 25–30% of women experience gastrointestinal side effects when first taking a bisphosphonate, the Committee agreed that it was important to consider the results of a sensitivity analysis assuming that 24% of women were experiencing bisphosphonate-related side effects in the first treatment month and 3.5% of women thereafter."

See appendix C of this overview for a complete list of the issues raised, and the August 2009 DSU report, 'annex 1' for the comments in full.

6.1.3 Summary of the DSU conclusions

The DSU was of the opinion that many of the comments from consultees and commentators did not relate to the functioning of the executable economic model but to the appropriateness of specific parameter values used in the model that were previously considered by the Appraisal Committee for these appraisals. It was noted that consultees and commentators would have been aware of these parameter values and been able to comment on them in previous consultations. The Appraisal Committee had previously concluded on the appropriate parameter values to adopt. The DSU therefore considered that these comments do not relate to the validity or functioning of the executable economic model and they were not investigated in detail.

The DSU agreed that some parameters in the executable model are fixed. These include those with small uncertainty, as well as those that are usually fixed in other models (such as standard mortality rates). The DSU emphasised that the WHO algorithm (which is academic in confidence) used to generate estimates of fracture risk was not embedded in the Assessment Group model. Rather, fracture risks computed using the WHO algorithm are

inputs in the model. Comparisons with fracture risks derived using the FRAX fracture risk calculation tool were made by several consultees, on the basis that the WHO algorithm supplied to the Assessment Group and in the FRAX tool are identical. It was not possible for the DSU to verify these analyses without access to the FRAX algorithm (which the DSU does not have), however, it confirmed that the estimates of fracture risk used in the economic model were consistent with those calculated using the WHO algorithm supplied to the Assessment Group by the data owner (as academic in confidence).

Sensitivity analyses conducted by the DSU suggested that none of the consultee comments relating to the modelling approach would lead to significant improvements in the cost effectiveness of the interventions, either cumulatively or in isolation. The DSU noted that in several instances the modelling approach adopted appeared favourable to the technologies; that is, the DSU suggested that the ICERs generated by the model may be underestimates.

The DSU concluded that it considered that none of the issues raised by consultees would either affect the validity of the model or raise justifiable doubts about the appropriateness of the use of the model to inform guidance.

7 Issues for consideration

Issues raised by the four consultees who provided comments on the Assessment Group executable economic model, included:

- criticism of the accessibility and transparency of the model, and an inability to validate it
- disagreement with modelling approaches
- disagreement with specific model inputs used.

Does the Committee accept the DSU's conclusions following the review of comments from consultees on the executable model?

In light of the individual comments from consultees on the model, the August 2009 DSU report and comments from consultees on the DSU report, does the Committee want to make any amendments to the current recommendations and/or other sections of the guidance on the primary and the secondary prevention of osteoporotic fragility fractures in postmenopausal women (TA160 and TA161)? If so, what are they?

In light of the individual comments from consultees on the model, the August 2009 DSU report and comments from consultees on the DSU report, does the Committee consider that further analyses to assess the validity of the Assessment Group's economic model should be conducted?

What is the Committee's view on the review date for TA160 and TA161, which is currently July 2010?

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October 2009

Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment reports for these appraisals were prepared by the School of Health and Related Research, University of Sheffield (ScHARR). Additional analysis reports were prepared by the Decision Support Unit (DSU), ScHARR:

- Stevenson M and Wailoo A (2009) A review of comments submitted by consultees on the economic model (August 2009 DSU report).
- Stevenson M (2008) Analyses of cost-effective BMD scanning and treatment strategies for generic alendronate, and the cost-effectiveness of risedronate and strontium ranelate in those people who would be treated with generic alendronate (February 2008 DSU report).
- Lloyd Jones M (2008) Critique of evidence put forward by Servier suggesting an association between acid-suppressive medication and fracture risk (February 2008 DSU critique).

B Pro-forma comments on the Assessment Group executable economic were received from the following organisations:

I Manufacturers/sponsors

- Servier

II Professional/specialist, patient/carer and other groups:

- Bone Research Society
- Society for Endocrinology
- National Osteoporosis Society

Appendix B: History of the appraisals

Year	Date	Event
2002		NICE receives remit to appraise alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention of osteoporotic fragility fractures in postmenopausal women. NICE begins by starting one appraisal to consider both primary and secondary prevention.
	November	Submissions are received from consultees
2003	March	**Technology Assessment Report (TAR) produced by the School of Health and Related Research, University of Sheffield (ScHARR) − the 2003 TAR − is issued for consultation** A read only version of ScHARR's economic model is available to consultees on request
	March	Comments are received from consultees on the 2003 TAR
	April	The Appraisal Committee meets and requests further analysis from NICE's Decision Support Unit (DSU) on raloxifene to inform its considerations
	October	The resulting DSU report and addendum 1 to the 2003 TAR, produced by ScHARR, are released for consultation
	December	**The Committee meets and an appraisal consultation document (ACD) is published − the 2003 ACD.** The DSU report and addendum 1 comments are published in an evaluation report

Year	Date	Event
2004	12 February	**The Committee meets and decides to split the appraisal into two parts; one for primary prevention and another for secondary prevention.** The same Committee would deal with each appraisal. The Committee would begin with secondary prevention first, as this was easier to deal with in the absence of the data from the anticipated World Health Organization (WHO) study and because information on identification of women at high risk of primary fracture was lacking. For secondary prevention, additional analysis was requested by the Committee. This later formed addendum 2 to the 2003 TAR.
	7 April	**The Committee meets and decides on an ACD for the secondary prevention of fracture − the 2004 (secondary prevention) ACD**
	27 April	ACD for the secondary prevention of fracture is issued for consultation Addendum 2 to the 2003 TAR (covering remodelling based on the Holt data) is published in the evaluation report
	June	**NICE receives the remit to appraise the cost effectiveness of strontium ranelate in the prevention of osteoporotic fragility fractures – the strontium ranelate appraisal** This began as a stand-alone appraisal for the use of strontium ranelate for primary and secondary prevention and continued as such until in April 2005, when it was combined with the appraisal of alendronate, etidronate, risedronate, raloxifene and teriparatide.
	8 June	**The Committee meets and a final appraisal determination (FAD) on the use of alendronate, etidronate, risedronate, raloxifene and teriparatide for secondary prevention is published – the 2004 (secondary) FAD.**
	October	The NICE Appeal Panel decides not to uphold an appeal against the 2004 (secondary prevention) FAD brought by Eli Lilly
	Late 2004	Professor Kanis provides the WHO algorithm to Matt Stevenson at ScHARR on condition that this data be kept confidential

Year	Date	Event
2005	January	**The 2004 (secondary) FAD is published as NICE technology appraisal guidance 87 (TA87)**
	January	Submissions are received for the separate strontium ranelate appraisal
	March	**The TAR concerned with the use of alendronate, etidronate, risedronate, and raloxifene for primary prevention – the 2005 (primary) TAR – is issued for consultation.** The TAR does not consider strontium ranelate. It also does not consider the WHO data because this had not been made available in time to be included.
	12 April	ScHARR presents a modelling update including the WHO algorithm at the Committee meeting. **NICE decides to integrate the appraisal of strontium ranelate with the appraisal of alendronate, etidronate, risedronate, raloxifene and (in relation to secondary prevention) teriparatide.** The aim was now to issue guidance on primary prevention for all drugs using the WHO algorithm in the economic model. The Committee would also carrying out a review of the extent to which the existing secondary prevention guidance (TA87) needed updating, and include an appraisal of the use of strontium ranelate for secondary prevention in that review.
	3 June	Stakeholders were informed of the new structure of the appraisals

Year	Date	Event
	July	The TAR that had been commissioned to inform the stand-alone strontium ranelate Appraisal is issued for consultation − the **2005 strontium ranelate TAR**. The economic model used in this TAR included the WHO data. The decision to merge the appraisals came too late for the main body of the 2005 strontium ranelate TAR to refer to the other drugs being appraised (alendronate, etidronate, risedronate, and raloxifene). However, these drugs were dealt with in a separate addendum − the 2005 addendum ScHARR's economic model now included the WHO algorithm.
	12 August	Corrections to and further analysis on the strontium ranelate TAR are provided by the Assessment Group
	6 September	The Committee meets to decide the content of the ACDs on the use of all drugs for primary prevention and the use of all drugs for secondary prevention − the 2005 ACDs
	30 September	**The 2005 ACDs are published for consultation** The Assessment Group's responses to the comments made on the 2005 strontium ranelate TAR are published as part of the evaluation report
	November	The Committee requests additional analysis.
2006	July	The **July 2006 report** is issued
	August	Comments received on additional analysis 1 are received from stakeholders.
	1 September	The price of alendronate drops to £173 per year. The Assessment Group provides new modelling results in the **September 2006 report**.
	6 September	The Committee meets to consider the new reports and agree the content of the ACDs for both primary and secondary prevention – the **2006 (primary) ACD** and **2006 (secondary) ACD**

Year	Date	Event
	21 September	The 2006 ACDs are published for consultation
	October	Comments from stakeholders are received on the 2006 ACDs
	October	Price of alendronate drops to £95 per year; the Assessment Group provides new modelling results in the **November 2006 report**.
	November	The Committee meets, no FAD is issued.
2007	February	The Committee meets to discuss the content of further ACDs on both primary and secondary prevention – the **2007 (primary) ACD** and **2007 (secondary) ACD**
	February	**The 2007 ACDs on primary and secondary prevention are issued for consultation** Following discussion within NICE and with the GDG for the Osteoporosis clinical guideline, these ACDs only dealt with the initiation of treatment. They did not deal with second-line treatment - that is, what treatment should be given if, for whatever reason, the recommended first treatment is not appropriate.
	April	Committee meeting to produce FADs
	June	**FADs on primary and secondary prevention are issued to consultees for appeal** – the **2007 (primary) FAD** and **2007 (secondary) FAD** NICE's responses to comments on the 2007 ACDs are published on the website
	July	**Some consultees appeal against the 2007 FADs**
	October	Appeal hearing
	11 December	The NICE Appeal Panel publishes its decision Some appeal points are upheld and the appraisal is referred back to the Committee

Year	Date	Event
2008	Early 2008	FRAX and a paper arising out of the WHO study is published, but does not include the details of confidential information that fed into the economic modelling from 2005 onwards
	January	The price of alendronate falls again, to £53 per year
	28 January	Stakeholders are updated on the outcome of the appeal
	23 January	NICE approaches Professor Kanis to request permission to release the confidential information.
	6 March	The Committee meets and decides on the content of the ACDs. The February 2008 report uses the updated price of alendronate (£53) and investigations into the potential effects of acid-suppressive medication are carried out in sensitivity analyses.
	25 March	**ACDs on primary and secondary prevention are released for consultation** – the **2008 (primary) ACD** and **2008 (secondary) ACD** The **February 2008 DSU report** (updated cost effectiveness results) is published. A critique of the information related to potential increased fracture risk linked to acid suppressive medication evidence is also published – the **February 2008 DSU critique**
	19 May	Professor Kanis clarifies that he refuses to permit NICE to release the confidential information
	1 May	The Committee meets to finalise the **2008 FADs**
	30 June	**FADs on primary and secondary prevention are issued for appeal –** the **2008 (primary) FAD** and **2008 (secondary) FAD** NICE responses to comments on the 2008 ACDs are published
	July	Appeals are lodged against the 2008 FADs

Year	Date	Event
	15 September	The Servier appeal against the 2008 FADs is heard by the **NICE Appeal Panel**
	30 September	NICE informed of Appeal Panel decision
	27 October	**Guidance published for primary (TA 160)** and **secondary (TA 161) prevention**
	Late 2008	**Servier application for Judicial review**
2009	20/21 Jan	Judicial review hearing
	March	**Court Order issued to NICE** The Court agreed that NICE was correct in not releasing confidential information, but considered that further negotiations could be undertaken by NICE to secure agreements to permit consultation on the model containing confidential data
	April	Communication with Professor Kanis results in agreement for release of model inclusive of confidential information – only for the purposes of commenting on the model and only to consultees complying fully with additional confidentiality undertaking
	April	Court Ruling – comes into effect
	9 April	Offer to consult on model issued to consultees and commentators (in order to fulfil Court Ruling)
	15 April	Servier application to Court of Appeal
	8 May	**Model consultation** begins (8-week period)

Year	Date	Event
	3 July	Comments on model received from: 1. Servier 2. Bone Research Society 3. National Osteoporosis Society 4. Society for Endocrinology
	July – August	DSU report on comments on model produced – **August 2009 report**
	14 August	**DSU August 2009 report sent to consultees and commentators for consultation** Consultees and commentators informed that release of further in confidence information to be requested from the owner, Professor Kanis.
	9 September	Consultee comments received on DSU August 2009 report.

Appendix C: List of issues raised in comments on the Assessment Group executable economic model

Consultee	Issues raised
Servier	1. Transparency and validation 2. Hip fracture estimates 3. Body mass index (BMI) 4. Intake of alcohol 5. Weighting of risk factors 6. Time horizon 7. Risk multipliers for fracture risk 8. Discount rates 9. Compliance 10. Side effects 11. Costs of fracture 12. Quality of life (QOL) for vertebral fractures 13. Cost-effectiveness of identification strategies
Bone Research Society	1. Alendronic acid assumed to have 10-fold the actual risk of side-effects that reduce QoL 2. British women assumed to be at far less risk of osteoporosis at a given age than shown by the observational data, making identification less cost-effective than is actually the case 3. ICERs assumed to be identical for all subgroups of women in a 5-year age band, irrespective of their BMD-independent risk factors. This excludes women with non-BMD-related higher than average risk from treatment 4. Absence of modelling of continuous variables known to the GP that confer risk independently of BMD 5. Distribution of BMD values according to number of CRF 6. Inadequate documentation of the model 7. Alcohol intake (rationale for the choice of 4 or more units per day intake is not justified) 8. Smoking and glucocorticoids [appear to be included in model, but not considered relevant in appraisal] 9. Lack of interactions between risk factors in the model

Consultee	Issues raised
National Osteoporosis Society	1. Clarity of the model 2. Population data 3. Inflation of side-effect disutility 4. Clinical risk factors 5. Alcohol clinical risk factor 6. Sensitivity analysis (BMI, time horizon, fracture risk calculation)
Society for Endocrinology	1. Complexity of data 2. Stalled clinical guidance 3. Cost reduction