National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

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

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

The economic model enclosed and its contents are confidential. The model is protected by intellectual property rights owned by the School of Health and Related Research, University of Sheffield. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the NICE Confidentiality Acknowledgement and Undertaking Form that has already been signed and returned to the Institute by your organisation and the undertakings given to Professor Kanis.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. You must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other than informing your comments.

Please set out your comments on the model in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response, and only responses on this pro forma will be considered.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to comment on the economic model itself. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as indicated below (please add further tables if necessary).

May 2009

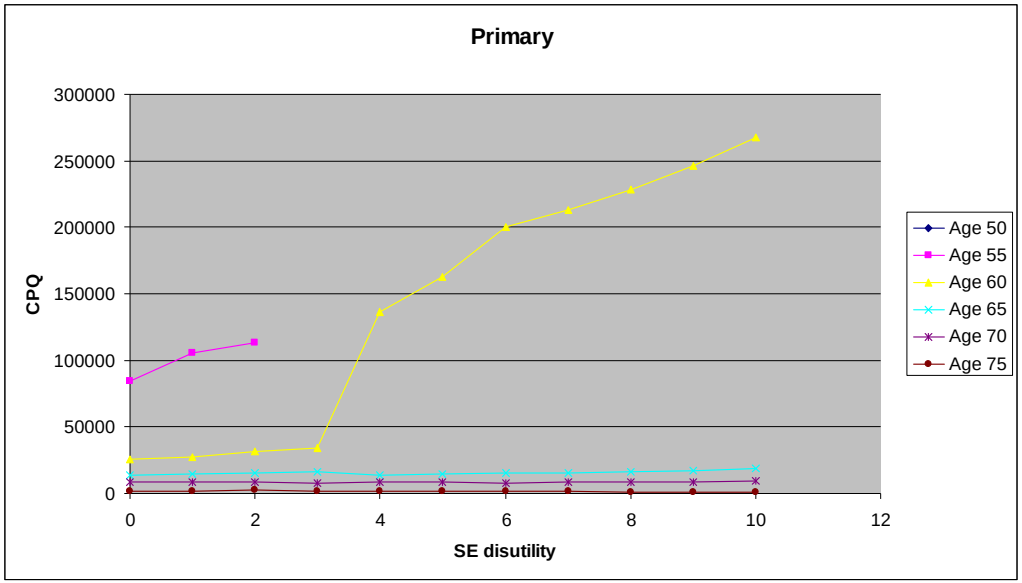
Issue 1 Clarity of the model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The instructions provided and comments within the spreadsheets of the model fall well short of transparency. The information provided is extremely limited and forms a substantial barrier to the charity providing meaningful comment on the economic model.	As a matter of record, the model needs to be fully documented and interpretable by external users.	N/A

Issue 2 Population Data

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In correspondence with NICE during the consultation period the National Osteoporosis Society asked for further information with regards the population data. We were subsequently provided with the original individual patient simulation model but informed that it was not used in formulating current TA 160/161 guidance. It appears that the distribution of BMD in the NICE model differs quite markedly from published data within the UK. The source of the population data is unclear.	Provide more information on the patient simulation model used within TA 106/161 to allow us to fully execute the model. Adjust the population distributions of BMD to accurately reflect the observed distribution in the UK	The ICERs will improve.

Issue 3 Inflation of side effect disutility

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
A Side effect disutility factor of 10 has been used in the model. In an evidence based setting, there appears to be a complete lack of evidence to support the use of this assumption. It has a dramatic effect on the ICER within younger women in the prevention setting with a threshold effect at an SE disutility multiplier of 4 (which is still not justifiable from the literature). An explanation of the marked effect beyond a multiplier of 4 at younger ages needs to be provided – it is not apparent from the model why this should be the case.	Return the SE disutility factor to the evidence based estimates (i.e. a multiplier of 1)	Primary SE Disutility Factor / 10 / 1 Age 50 / / Age 55 / / £105,301 Age 60 / £267,460 / £27,534 Age 65 / £18,391 / £14,542 Age 70 / £9,290 / £8,199 Age 75 / £1,060 / £2,084 

		Secondary SE Disutility Factor: 10 / 1 Age 50: £ 26,894 / £ 25,424 Age 55: £ 18,333 / £ 17,914 Age 60: £ 14,806 / £ 13,950 Age 65: £ 6,211 / £ 9,142 Age 70: £ 3,389 / £ 2,823 Age 75: -£ 2,369 / -£ 1,659

Issue 4 Clincal risk factors

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The model uses a number of risk factors (current smoking, corticosteroid use previous or current) that are not included in the guidance.	Incorporate these risk factors into the guidance and/or produce separate guidance for glucocorticoid users	Incorporating smoking as a risk factor in the guidance would acknowledge the increased risk that the 21% of women aged 50-59 and 12% of women aged 60+ who smoke have[1]. This will ensure that they receive the appropriate treatment commensurate with their fracture risk. [1]http://www.statistics.gov.uk/downloads/theme_compendia/GHS07/GHSSmokingandDrinkingAmongAdults2007.pdf

Issue 5 Alcohol CRF

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Within the guidance an alcohol intake of 4 or more units per day is used. However the model appears to use an intake of greater than 2 units per day. The coefficient for the	Ensure that there is consistency between the guidance and information used within the economic model. Use appropriate thresholds and their associated coefficients.	N/A

latter will be inappropriately low for the 4 unit threshold and underestimate fracture risk. Again, the documentation of the choice of a 4 unit threshold is sadly lacking and is an extremely rare occurrence in post-menopausal women in the UK.		

Issue 6 Sensitivity Analysis

Description of problem	**Description of proposed amendment**	**Result of amended model or expected impact on the result (if applicable)**
The model as supplied does not permit alterations to a number of elements preventing sensitivity analysis 1. Body mass index (BMI) is set at a fixed value. This is not consistent with the construct of FRAX® and the gradient of fracture risk rises dramatically as BMI falls, independent of other risk factors such as age.	Amend model to allow sensitivity analysis of varying BMI	This will improve the accuracy of all risk estimates (other than the current fixed value of 26kg/m^2).
2. The NICE model uses predominantly a ten-year time horizon which has a large effect on apparent cost-effectiveness. There are no data that test the sensitivity of the NICE model to changes in the time horizon and no way to test the adequacy of the bolt-on calculations made to remedy the deficit in the model.	Amend model to allow sensitivity analysis of varying time horizon	
3. The model is populated with pre-specified clinical risk factor estimations, so that sensitivity analysis around the assumptions cannot be performed.	Amend model to allow sensitivity analysis of varying CRFs	

(Please cut and paste further tables as necessary.)