National Institute for Health and Clinical Excellence

Denosumab for the prevention of osteoporotic fractures in postmenopausal women

Response to consultee and commentator comments on the draft remit and draft scope

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Bone Research Society	Arguably less appropriate than for secondary prevention, since given the likely cost of denosumab it's use in primary prevention seems unlikely	Noted. Primary or secondary prevention is not specified in the remit referred by the Department of Health (DH). Furthermore, the Appraisal Committee does not consider the affordability, that is, costs alone of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources.
	National Osteoporosis Society	The National Osteoporosis Society feels it is appropriate to refer this topic for appraisal by NICE.	Noted.
	British Society for Rheumatology	Appropriate. However the results of the phase III trials reporting fracture reduction with denosumab must be published prior to the start of this appraisal to ensure that all relevant data are included	Noted. The workshop discussed the availability of evidence and outcomes appropriate to appraisal of denosumab. The workshop noted that at least two phase III studies have been published. It was agreed that bone mineral density (BMD) as well as fracture rate would be outcomes relevant to the appraisal.

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	Novartis Pharmaceuticals	No comments	Noted.
	Royal College of General Practitioner	Highly appropriate. Osteoporotic fractures create a huge burden on patients in terms of excess mortality and loss of HRQoL as well as a major impact on health and social care utilisation. This is a novel therapy with a new route of administration that may overcome recognised difficulties patients have with adherence, persistence and concordance with existing appraised therapies for this clinical area	Noted. Mortality and health related quality of life (HRQoL) are included in the scope. The reference case stipulates that the perspective adopted on cost should be that of the NHS and PSS. Adverse effects of the technology and comparator treatments are included in the scope. The 'other considerations' section of the scope has been revised to highlight consideration of continuation of treatment.
	Amgen	We agree that it is appropriate to refer this topic to NICE for appraisal.	Noted.
Wording	BRS	Seems appropriate	Noted.
	NOS	Yes	Comment unclear.
	BSR	No. The remit should include both primary and secondary prevention of osteoporotic fractures. Currently the remit only has primary prevention. The marketing authorisation should help determine this.	Noted. Guidance will only be issued in accordance with marketing authorisation. Primary or secondary prevention is not specified in the remit referred by DH.
	Novartis	No comments	Noted.

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	RCGP	Broadly yes, though the effect on BMD is much less relevant clinically than fracture outcomes. The scope might like to also consider 1) The offset of effect 2) The likely consequences of the dosing frequency and route of administration on compliance and persistence	The workshop discussed the clinical relevance of fracture outcomes. It was agreed that BMD outcomes were also relevant to the appraisal. 1. 'Offset' of costs of intervention on potential savings on other costs of care will only be considered if these are within the reference case. 2. The 'other considerations' section of the scope has been revised to highlight consideration of continuation of treatment.
	Amgen	The wording of the remit does reflect the issues of clinical and cost effectiveness that NICE should consider.	Noted
Timing Issues	BRS	Densosumab is likely to be licensed in 2009 and so some urgency to complete appraisal as there is likely to be pressure to prescribe it.	Noted. The commencement of the appraisal at this time has the potential to produce timely guidance for the NHS.
	NOS	It is important that the appraisal is completed in a timely manner to ensure that patients have a range of cost-effective treatments availiable to them.	Noted. Please see immediately above.
	BSR	Suggested timing is appropriate assuming phase III fracture reduction studies are published	The workshop noted that at least two phase III studies have been published and others are completed or ongoing.
	Novartis	No comments	Noted.

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	RCGP	I cannot see any suggested timing but ideally any guidance should be ready by product launch	Noted. The commencement of the appraisal at this time has the potential to produce timely guidance for the NHS.
	Amgen	We anticipate being able to make an evidence submission from **the latter half of** November 2009.	Noted. Please see immediately above.
Additional comments on the draft remit	BRS	Might want to add the intention to explore high risk subgroups in which denosumab is more likely to be cost effective	The 'other considerations' section of the scope lists subgroups of people in whom the technology may be particularly cost effective. Specific reference is made to risk of fracture.
	BSR	None.	Noted.
	RCGP	Should consideration be given in the consultattion to incorporating this potential TA within 160 and 161	The proposed appraisal will be distinct from existing guidance, but comparators will be determined by the recommendations of the Technology appraisal guidance Nos. 160 and 161.
	Amgen	No	Noted.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	BRS	Bisphosphonates and SERMs both act to slow bone loss by suppressing bone resorption (the suggestion that SERMs stimulate bone formation like PTH is erroneous)	Noted. The scope has been revised and no longer describes mode of action of comparator technologies.
	NOS	The section on drug treatments contains errors. Correct to: Bisphosphonates and SERMs act to slow bone loss; parathyroid hormone stimulates bone formation and strontium ranelate probably works by strengthening bone material properties.	Noted. Scope revised as above.
	BSR	The last paragraph of the background listing the various drugs for treatment of osteoporosis and describing their actions has inaccuracies. It may be best just to list them rather than attempt to summarise their modes of action.	Noted. Scope revised as above.
	Novartis	No comments	Noted.
	RCGP	Sufficient for the broad representative bodies	
	Amgen	We have no additional comments on the background other than the comparators proposed, see notes below	Noted.
The technology/ intervention	BRS	Might be worth adding that denosumab is the first biological therapy which targets osteoclastic bone resorption. Could also add that denosumab has been found to halt erosive progression in rheumatoid arthritis (RA)	Noted. Only a brief description of technology class and mode of action are normally included in scopes. The clinical and cost effectiveness of this new technology will be appraised in accordance with the Single Technology Appraisals process.
	NOS	Yes	Noted.

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	BSR	Yes although in the final sentence it would be more correct to say that the drug has been studied "….in postmenpausal women with low bone mineral density AND FRACTURES compared to placebo and alendronate." Up to 23 % of patients in the latest trial (FREEDOM) had prevalent vertebral fractures	The workshop discussed the availability of evidence for women with fractures. The details of the evidence will be assessed and appraised during the course of the appraisal.
	Novartis	No comments	Noted.
	RCGP	Sufficient	Noted.
	Amgen	Please add the following additional information to the description of the technology: Denosumab (AMG 162) is a fully human monoclonal antibody that specifically targets the receptor activator of nuclear factor kappa B ligand (RANKL) and neutralises its activity, thereby inhibiting osteoclast differentiation, activation, and survival. Increased osteoclast activity is critical in the pathogenesis of osteoporosis.	Noted –the nature of the technology (as described in this comment) was discussed at the workshop. Only a brief description of technology class and mode of action are normally included in scopes.
Population	BRS	It would be helpful to define readily identifiable sub-populations in which cost effectiveness is likely to be increased eg patients with concomitant RA	The 'other considerations' section of the scope lists subgroups of people in whom the technology may be particularly cost effective.
	NOS	Postmenopausal women, the largest group of patients with osteoporosis, is an appropriate population for this appraisal. However, we feel that men and premenopausal women should not be left without treatment options.	Noted. Guidance will only be issued in accordance with marketing authorisation.
	BSR	Appropriate	Noted.
	Novartis	No comments	Noted.

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	RCGP	Sufficient, but going forward about 35% of hip fractures occur in men and this proportion is rising. There is a clinical, demographic and an equality imperative about considering fragility fracture prevention in men as they suffer higher morbidity and mortality	Noted. Potential equalities issues were discussed at the scoping workshop. It was noted that the evidence base is in postmenopausal women. The remit is limited to women. Guidance will only be issued in accordance with marketing authorisation.
	Amgen	We agree that the population is appropriately defined.	Noted.
Comparators	BRS	Comparators for RA would need to consider patients treated with conventional disease modifying agents and biological therapies like anti-TNF separately, as these have different efficacies in terms of preventing erosive progression.	Noted. Consideration of specific subgroups may only depend on the availability of evidence. Guidance will only be issued in accordance with marketing authorisation.
	NOS	We feel that this should be clearly defined and propose the inclusion of zoledronate as its major comparator and alendronate as the first-line treatment defined by (TA160/161)	The scope has been revised to specify 'Bisphosphonates (such as alendronate, etidronate, risedronate, ibandronate, zoledronate)'.
	BSR	Should state generic alendronate	The appraisal will consider evidence of both clinical and cost effectiveness. Workshop participants agreed that denosumab should be appraised relative to the most appropriate and cost effective alternatives.
	Novartis	Specification of comparators as "management strategies without the use [of] denosumab" is somewhat ambiguous and implies that comparison to a "no treatment" strategy might be appropriate. The background information section of the scope lists a number of established drug treatments for the treatment of post-menopausal osteoporosis. We suggest that the scope reflects the background information section by listing appropriate active comparators.	Noted. The scope has been revised, so that only drug treatments are considered as comparators to denosumab. Strategies which do not include management without effecting bone metabolism are not included in the scope.

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	RCGP	I am not aware of any planned TA for ibandronate and zoledronate. Uncorrected this would leave a rather puzzling gap in the therapies for osteoporosis evaluated by NICE. Zoledronate IV, particularly could be seen as a near comparator with similar efficacy and a longer dosing interval.	The scope has been revised to specify ' Bisphosphonates (such as alendronate, etidronate, risedronate, ibandronic acid, zoledronic acid)'.
	Amgen	The draft scope lists all drug treatments for osteoporosis in the background section of the scope but does not list any specific comparators for denosumab in this section. The table states that comparators are 'Management strategies without the use of denosumab'. As recently published NICE guidance (TA No. 160) recommends the use of alendronate, risedronate, etidronate, and strontium ranelate for this population, we anticipate these therapies are therefore considered standard treatments in the NHS with which denosumab should be compared.	Noted. The scope has been revised, so that only drug treatments are considered as comparators to denosumab. These include the technologies considered in TA 160 and 161.
Outcomes	BRS	For fragility fractures, outcomes need to be considered separately for patients with hip fracture, vertebral fracture, and other non vertebral fracture, as these have distinct health economic consequences. Might also want to include erosive progression in RA.	Consideration of specific subgroups may be dependant on the availability of evidence.
	NOS	Yes	Comment unclear.
	BSR	Having BMD as an outcome may be problematic as changes in BMD are not necessarily strongly associated with changes in fracture rates	It was agreed at the scoping workshop that bone mineral density (BMD) as well as fracture rate would be outcomes relevant to the appraisal.
	Novartis	No comments	Noted.
	RCGP	BMD will not capture health related oucome measures	HRQoL outcomes are specified in the scope.
	Amgen	The clinical outcomes are appropriately defined	Noted.
Economic	BSR	None	Noted.

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analysis	NOS	A life time horizon should be used in the modelling. The clinical endpoint used should be fragility fracture, and not limited to patients with osteoporosis. Fracture risk should be defined as fracture probability.	Noted. The NICE reference case states that time horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The workshop discussed the appropriate population to include in the scope and the definition of osteoporosis and osteoporotic fractures. The workshop heard from clinical specialists and the manufacturer that 10 year fracture probabilities were becoming established in clinical practice and specified in regulatory body guidelines. The 'other considerations' section of the scope has been revised to highlight consideration of assessment of probability of fracture.
	Novartis	No comments	Noted.
	RCGP	Current risk prediction technologies and health economic analysis tends to be over ten years. Are the true costs of NHS fracture care included within the analysis (as opposed to tariff costs)? Are the best estimates of social care included (see NCCHTA 2002, Kanis et al.)?	The 'other considerations' section of the scope has been revised to highlight consideration of assessment of probability of fracture. Economic evaluation should conform to the NICE reference case. For more information see the Guide to the Methods of Technology Appraisal 2008: www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459

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	Amgen	If this appraisal proceeds, Amgen propose to submit an economic evaluation for denosumab according to the reference case analysis provided by NICE. Such an analysis would provide cost effectiveness estimates for denosumab compared to the standard treatments already recommended by the Institute, where appropriate. We note that the economic model used to develop the current recommendations within TA160 is not publically available, and inputs to that model remain unpublished. We therefore note that it may be difficult to achieve accurate alignment between any new analyses provided by Amgen with the Institute's published recommendations. We would be grateful if the Institute could make comment on this point at the scoping workshop.	Noted. NICE could not release the model as it used data which is restricted as academic in confidence by a party external to NICE. In 2009, the Assessment Group's executable economic model was released for consultation to parties agreeing to additional undertakings with the owner of confidential data.
Equality and Diversity	NOS	The charity welcomes further appraisals of treatments for osteoporosis. This will allow patients to have a range of treatment options if age or abililty precludes a particular therapy. The population defined in the scope excludes men which could lead to inequality in treatment between genders.	Noted. Potential equalities issues were discussed at the scoping workshop. It was noted that the evidence base is in postmenopausal women. The remit is limited to women.
	BSR	None	Noted.
	Novartis	No comments	Noted.
	RCGP	Any potential TA should fully and completely align to the principles of equality statutorily embedded in NICE procedures. Disability legislation should not be 'trumped by health economic arguments.	Potential equalities issues were discussed at the scoping workshop. It was noted that the evidence base is in postmenopausal women. The remit is limited to women. The scope also highlights consideration of people with a disability which prevents them from using specific technologies.
	Amgen	No comment	Noted.
Other	NOS	No additional issues.	Noted.

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considerations	BSR	None	Noted.
	Novartis	No comments	Noted.
	RCGP	The potential TA should probably map to other NICE guidance such as the draft or final CG on medicines concordance	Noted. Technology appraisals (TA) generally have more focused scope than Clinical Guidelines (CG). At scoping stage, some clinical guidelines may specify that they will incorporate technology appraisals, others may be scoped to supersede existing technology appraisals. The scope has been revised to highlight consideration of continuation of (concordance, persistence) treatment.
	Amgen	No comment	Noted.
Questions for consultation	NOS	These are covered in the above sections.	Noted.
	BSR	- The population needs to be defined similar to previous NICE guidance in this disease area - There should be separate consideration given for primary and secondary prevention - Most of the focus should be on the ouctome of fracture reduction	Noted. Primary or secondary prevention is not specified in the remit referred by the Department of Health (DH). The workshop discussed the clinical relevance of fracture outcomes. It was agreed that BMD outcomes were also relevant to the appraisal. Fracture and BMD outcomes are specified in the scope.
	Novartis	No comments	Noted.

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	RCGP	Should the scoping consultation consider the necessity of any potential recommendations being in terms that are easily implementable in clinical practice? Should consideration be given therefore to the advantages and disadvantages of basing intervention recommendations on absolute fracture risk prediction derived from FRAX informed by BMD. rather than complex interactionbs between a selection of two classes of risk factor and BMD?	Noted. The scope has been revised to highlight consideration of assessment of probability of fracture.
	Amgen	The STA process is appropriate for this proposed appraisal topic if recommendations for denosumab compared to therapies currently recommended by the Institute are considered valuable to the NHS. If wider recommendations are desired, to include therapies in use but not considered by the Institute in its existing recommendations, then an MTA process or evaluation within a clinical guideline would be required. We note the guideline 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk' is currently suspended. If during this consultation the issues of appraisal are wider than those outlined in this scope, then further economic evaluation in osteoporosis may be optimally considered within the context of a clinical guideline.	Noted. The workshop discussed the options available for appraisal of denosumab. The workshop agreed that denosumab would be appropriate for the STA process. It was also noted that an STA may have the potential to produce timely guidance for the NHS.
Additional comments on the draft scope.	NOS	In addition to the appraisal of Denosumab the charity would welcome appraisals of Zoledronate, ibandronate and Preotact.	The scope has been revised to specify ' Bisphosphonates (such as alendronate, etidronate, risedronate, ibandronic acid, zoledronic acid)' and 'Selective oestrogen receptor modulators'.

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	Novartis	In addition to any completed or proposed technology appraisals of selected agents for the treatment of post-menopausal osteoporosis, there remains a significant opportunity for NICE to develop a comprehensive clinical guideline that covers all currently available treatment options for all patient populations at risk of osteoporotic fractures (i.e. not just post-menopausal women). In this respect, it is disappointing to note in the section in the draft scope on "related NICE recommendations" that the NICE clinical guideline on osteoporosis remains “suspended”. In the absence of a timely and comprehensive national guideline on the risk assessment, diagnosis and management of patients at high risk of osteoporotic fractures, there is potential for patients to receive suboptimal care.	Noted. The workshop agreed that denosumab would be appropriate for the STA process. It was also noted that an STA may have the potential to produce timely guidance for users of the NHS.
	BSR	None	Noted.
	Amgen	No	Noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

BPS
MS
NHS QIS
NPHS
Proctor and Gamble
RCPhys*
RCN
RICE
WAG
RCPCH

*Royal College of Physicians endorsed comments submitted by the BSR