National Osteoporosis Society

Camerton, Bath BA2 0PJ
Tel: 01761 471771
Fax: 01761 471104
helpline: 0845 450 0230
website: www.nos.org.uk
e.mail: info@nos.org.uk

23rd April 2008

Dr Carole Longson
Director, Centre for Health Technology Evaluation
MidCity Place
71 High Holborn
WC1V 6NA

Dear Carole,

Appraisal consultation documents on technologies for the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women

The National Osteoporosis Society thanks you for the opportunity to comment on Appraisal Consultation Documents (ACDs) further to the appeals on the final appraisal determinations for the primary and secondary prevention of osteoporosis.

The Society is extremely disappointed that despite the concerns that we have articulated in previous consultation responses, particularly on the 2006 ACDs for these appraisals, the recommendations remain too complex and are unworkable. The tables of thresholds for selecting each treatment are too complicated to use in practice, the use of two classes of risk factors is not an evidenced approach and the challenge of stopping treatment if a patient becomes intolerant of alendronate is unworkable.

Furthermore we are very concerned that NICE has failed to consider the recent publication of the World Health Organization (WHO) fracture risk assessment tool (FRAX) in its further consideration of these appraisals, even though undisclosed data "prepared under the auspices of the WHO" have been used in the context of the assessment group's economic modelling. This tool has been developed with support and input from world renowned experts, is endorsed by all of the major osteoporosis groups worldwide and is fully supported by the WHO. FRAX clearly represents the most accurate method currently available for the proper assessment of risk of fractures in osteoporotic patients. We simply do not understand why the appraisal is based on an incomplete measure of fracture risks in circumstances where FRAX now provides the standard approach for assessment. We believe that the approach currently followed in the ACDs, which disregards the significant development represented by FRAX is not in the best interest of patients or clinicians.

As many of our comments overlap between your suggested headings, as previously we have separated our comments on these ACDs into specific areas which reflect

our main points of concern. Where points relate to only one of the ACDs we specify which one accordingly.

Response to the appeal panel decision

We are pleased that NICE has reconsidered the inclusion of all of the technologies under assessment in these appraisals and that the ACDs now include recommendations for treatment for people for whom alendronate is contraindicated or who are unable to tolerate it. However, we do have a number of concerns about how the recommendations for alternative first line and second line treatments have been incorporated, which we refer to below.

Furthermore, there were a number of areas in the Appraisal Committee's assessment of the evidence where the appeal panel requested improved clarity and transparency. However, in important aspects the preliminary guidance in the two ACDs remains unclear and we therefore request further reasoning of the Committee's conclusion and/or disclosure of evidence, particularly in the areas identified below:

- One of the points advanced at the appeal, was that we were unable to find any proper explanation around the Appraisal Committee's approach to mortality benefits associated with osteoporosis treatments in the context of the assessment of cost effectiveness. The Appraisal Committee was therefore directed to provide clarification (as requested in paragraph 44 of the appeal panel's decision documents for both primary and secondary prevention). However, it remains unclear from the ACDs how the Appraisal Committee has taken benefit in terms of mortality into account in reaching its conclusions.
- We would also like further transparency around the use of the "ten times side effects" approach with reference specifically to raloxifene, strontium ranelate and teriparatide (secondary prevention only). The basis for the way in which such effects have been assessed and incorporated into the analysis is currently unexplained and we therefore request that clarification is provided in the next version of these recommendations.
- In the context of the requirement (set out in paragraphs 6.2.6.10-11 of the "Guide to the Methods of Technology Appraisal") to take into account various listed factors when considering whether a technology should be recommended in circumstances where the cost per QALY exceeds £20,000, it is clearly impossible for such factors to be adequately considered if the relevant cost per QALY figure has not been calculated. It is significant that the Appraisal Committee's conclusions with respect to the cost per QALY values for the various treatments, following the modifications to the evaluation report, are not provided in the ACDs. It is unclear whether or not the Appraisal Committee did in fact calculate the relevant cost per QALY values in order to put itself in a position to consider the cost effectiveness of these technologies in the various circumstances, described in the ACDs. Furthermore, it is impossible for the Society or other consultees to consider whether the proposed guidance contained in the ACDs fairly reflects the available evidence if the conclusions of the Appraisal Committee are incompletely expressed. In these circumstances, we would ask to be advised of the Committee's conclusions with respect to the costs per QALYs gained of the treatments and the circumstances under consideration, and to be given an opportunity to make submissions as to the validity of these findings before a final determination is issued.

Although the appeal was not upheld on any of the individual points that we raised regarding the inputs to the economic modelling, we remain concerned about the conservative approach taken in determining the assumptions that have been used. We believe that the sum of these decisions has resulted in NICE making very conservative draft recommendations for the treatment of people with this disease.

Classification of risk factors

We believe that the decision not to ensure that the recommendations could be used alongside FRAX is short-sighted and does not reflect how clinical practice is changing. The FRAX website is currently receiving around 23,000 hits every day and the publication of European guidelines will push this approach well into the operational arena.

In sections 4.3.32 (primary prevention) and 4.3.33 (secondary prevention) the Appraisal Committee have provided reasoning for their decision not to use FRAX, however we do not believe that this it is an adequate explanation. FRAX provides an approach to opportunistic case finding which will ensure that treatment is targeted to those who are most at risk of fracture. Although we acknowledge that there is only limited evidence to show that identifying patients by FRAX and treating them results in fracture risk reduction, McCloskey *et al* (2007) showed positive results when patients selected on the basis of fracture risk as assessed by FRAX were treated with clodronate on the basis of FRAX risk. We do not believe there is any evidence whatsoever for the approach that the Appraisal Committee are recommending. Indeed it encourages poor clinical practice and is now hopelessly out of date.

The way in which BMD dependent and independent risk factors are used in the ACDs still gives us considerable cause for concern and their use in women under 70 has produced inappropriate and unnecessary barriers to treatment. We do not believe that use of the two categories of risk factors in this manner is an evidence based approach and indeed this divide does not consider the weight of individual factors in determining fracture risk. For women aged 65-69 years who have not yet had a fracture, it is clinically inappropriate to ignore the presence of risk factors that are indicative of low BMD when determining who requires a DXA scan, given the importance of BMD in determining fracture risk. To deny women under 65 years, who have multiple indicators of low BMD, a DXA scan because they do not have an independent risk factor is again inappropriate. The Society urges the Committee to take a more pragmatic approach to the use of risk factors.

Additionally, while the so called “independent risk factors” used for the purposes of the economic modelling were based on WHO data, including but not limited to the factors listed in the ACDs at paragraphs 4.2.11 (primary prevention) and 4.2.12 (secondary prevention), the independent risk factors used by the Appraisal Committee to determine access to treatment (both ACDs) and DXA scanning (primary prevention) is limited to only some of those factors defined by the WHO data and some of those used for the purposes of economic modelling. This inconsistent approach appears arbitrary and the exclusion of certain established risk factors from those listed at paragraphs 1.5 of both ACDs, even though they are accepted by both the Assessment Group and the WHO as being significant, is unexplained. In particular we believe that the list of risk factors at paragraphs 1.5 and 2.12 of both ACDs should include:

- A wider range of conditions that cause secondary osteoporosis (including type 1 diabetes, thyroid disorders and organ transplantation for example).

- Use of prescribed medicines which are known to increase the risk of fracture (including aromatase inhibitors and some of the anti-epileptic drugs for example).
- Smoking; we remain unclear as to why the Appraisal Committee continues to fail to include current smoking as a risk factor, when smoking itself is included as a risk factor in the economic modelling (section 4.2.11 of the primary prevention ACD and 4.2.12 in the secondary prevention ACD). This approach will cause even more confusion now that FRAX has been published which does include smoking in its case finding approach.

We urge the committee to ensure that it is clear from the recommendations that any list of risk factors provided is not exhaustive and that clinical judgements should be exercised to ensure that persons with risk factors that have not specifically been identified are not subject to discrimination. For completeness, we believe that the current framework of the ACD, which is very prescriptive in terms of the limited conditions that may be taken into account as risk factors for fracture (when considering treatment) or as a risk factor for low BMD (when considering DXA scanning) discriminates against persons who do not have those particular factors, but an equal risk of fracture because of other aspects of their condition or circumstances not specifically recognised by NICE. We would therefore ask the Appraisal Committee to reconsider its position.

Treatment of patients for whom alendronate is contraindicated, who are intolerant of alendronate or who do not respond to it

In the recommendations sections of both ACDs we notice that the specific circumstances for using a second line treatment (patients who are unable to comply with the special instructions or who have a contraindication to or are intolerant of) fails to include those patients who fail to respond to treatment. Although we suspect that this would relate to a significant minority of patients, there should be provision within the ACDs for them to go onto a second or third line treatment. We suggest that this should be added into sections 1.2 and 1.3 of the primary prevention ACD and to sections 1.2, 1.3 and 1.4 of the secondary prevention ACD.

The Society believes that groups of patients who have a contraindication to alendronate will be discriminated against under the current draft recommendations. As this population will often be frail and elderly, failure to treat them, or the use of differential treatment thresholds, could be perceived as ageism. Furthermore, individuals who are unable to comply with the instructions for taking alendronate due to pre-existing medical conditions (for example Crohn's disease, neurological diseases such as Parkinson's and stroke patients) could be unable to benefit from fracture risk reduction unless they were at a much higher risk than patients without these disabilities. A 64 year old lady, who experienced a premature menopause and whose mother had a hip fracture, and who has a swallowing disturbance following a recent stroke would be ineligible for treatment. Her friend who has not suffered a stroke, but who has the same risk factors would receive a treatment to reduce her risk of fracture. Although this is a very specific example it clearly shows that the rigid application of risk factors to determine access to treatment will produce anachronistic and discriminatory results. In particular proposing different treatment methods for different medicines means that clinicians will be in a difficult position when it comes to treating people with disabilities, who are unable to take alendronate, under these technology appraisals.

We remain extremely concerned about the stepped intervention thresholds for second line treatments for all women. Imagine if you were told that you are very

likely to fracture due to osteoporosis (or perhaps have fractured) and have been prescribed generic alendronate. You have taken the treatment for a month but have had very uncomfortable side effects that have affected many aspects of your life. Imagine then returning to your GP and being told that you are going to have to wait for your bones to deteriorate over the next 2 or 3 years before you are bad enough to receive a freely available alternative therapy. Our members are outraged by this decision and the clinicians that we have consulted with during the preparation of this response believe that such a treatment strategy is unethical and would be poor clinical practice.

A woman who has been prescribed a first line treatment due to her high risk of fracture would be considerably fearful of fracture if denied a second line treatment. In this case a second line treatment is essential and the disutility associated with the fear of fracture and knowledge of the presence of this disease should be incorporated into the economic modelling.

The cost per QALY threshold for primary prevention

At paragraph 4.3.15 of the ACD for primary prevention, the Appraisal Committee states that a £20,000 cost per QALY threshold has been adopted in the case of primary prevention, because the population in question is "an asymptomatic group of adult patients".

- While, by definition, the patients eligible for primary prevention are asymptomatic, they suffer from a chronic disease which may result in osteoporotic fractures which "are associated with substantial disability, pain and reduced quality of life" (paragraph 2.6 of the ACD for primary prevention). The ACDs also recognise the lifetime risk of fractures in women over age 50 years and consider the very substantial morbidity and costs associated with osteoporotic fractures, particularly those of the hip. In view of the statement at paragraph 2.9 of the ACD that, following a hip fracture "a high proportion of women are permanently unable to walk independently or to perform other activities of daily living and consequently many are unable to live independently", we believe that the Appraisal Committee should reconsider the arbitrary imposition of a low £20,000 cost per QALY threshold for treatments that are intended to prevent such events occurring. It is, we suggest, inappropriate simply to categorise women who have not yet experienced an osteoporotic fragility fracture as being "asymptomatic" and the very substantial benefits in terms of preventing long term disability are self evident.
- Moreover, the imposition of a rigid cost per QALY threshold of £20,000 for patients who are currently asymptomatic from their disease, is inconsistent with the approach followed by the Appraisal Committee in the context of other appraisals. The appraisal that considered use of statin medication (TA94) assessed use of statins in the primary prevention of cardiovascular disease in patients who are asymptomatic. In that appraisal, there was no suggestion that the cost per QALY threshold should be limited to £20,000. In circumstances where the use of the QALY is intended to allow for comparison of different products across different therapeutic areas, we believe that similar criteria should be applied in relation to the primary prevention of osteoporosis as those applied in the statin appraisal.
- Furthermore, the statement that the population receiving treatment is "an asymptomatic group of adult patients" has less force when considering second line treatment for primary prevention. These patients are women who

have already been diagnosed as suffering from osteoporosis and received treatment and accordingly the withdrawal of effective therapy may cause active harm to such patients.

In the latter case we would strongly encourage the appraisal committee to, at a minimum, adopt a cost per QALY threshold of £30,000 per annum for second line treatment in the primary prevention ACD, as for secondary prevention.

The positioning of etidronate as an alternative to risedronate

The positioning of etidronate as a direct alternative to risedronate as a second line treatment is misleading. We commented on this in our response to the October 2006 ACDs noting that although we accept that etidronate is low cost we strongly question its prominence as an alternative first line treatment simply on economic grounds. Due to the lack of evidence for non-vertebral and hip fracture risk reduction we believe that the prescription of etidronate to many patients would be inconsistent with proper clinical care. At a minimum we would suggest that the following statement is included in both ACDs:

"When choosing which treatment to prescribe the decision should be made on consideration of the treatment's efficacy and in consultation with the patient"

Release of the Economic Model and the WHO data used for the purposes of the cost effectiveness assessment

In their findings, the appeal panel asked the Guidance Executive to request permission from the WHO to release the Institute from its undertakings relating to the academic-in-confidence data used to populate the economic model underpinning these appraisals. Further to the publication of FRAX, we requested a copy of the economic model in correspondence with you on 21st February 2008 and also by email on 11th April 2008 (sent to [redacted]) on behalf of the Society. We eventually received a response by email on Friday 18th April, which noted that:

"We (NICE) *have sought permission from* [redacted] *for the epidemiological data, which have fed into the economic model, to be released from the academic-in-confidence agreement.* [redacted] *has replied that he does not wish to release NICE or ScHARR from the obligation to keep in confidence the information previously supplied. Although we do not regard this as a satisfactory situation, we are not in a position to override the wishes of the owner of the data"*

However, we were under the impression that [redacted] is willing to make the algorithms available to NICE. We would welcome clarity on this matter as soon as possible as this issue continues to prevent us from fully considering the evidence behind these appraisals and has again limited our ability to comment on the economic modelling.

Review Date

The review date for both documents is July 2010. We believe that these documents will require review much sooner as they have failed to consider the impact of FRAX on clinical practice. Additionally with zoledronic acid, ibandronic acid and recombinant parathyroid hormone all now licensed for the treatment of osteoporosis, there is a need to further update the guidance positioning these treatments accordingly.

Although we have tried to be constructive in our approach to this consultation, it is becoming increasingly difficult for us to work with our stakeholders when developing our response. Many people feel that the NICE process is not working in the best interest of patients and they are now reluctant to contribute as they do not feel that their views will be seriously considered. In particular, the clinical community feel that the draft guidance is totally unworkable and that it encourages poor clinical practice which would be unethical. We urge NICE to ensure that they include osteoporosis specialists in the discussions at the next Appraisal Committee meeting to ensure that they can work with the Committee to improve clinical workability.

We hope that these comments will be helpful in your further consideration of these ACDs and of course if we can be of any additional help, please do not hesitate to contact me.

Yours sincerely

For and on behalf of the National Osteoporosis Society