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18th August 2005

Dr Carole Longson, Director
Centre for Health Technology Evaluation
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London, WC1V 6NA

Dear Dr Longson

Re: The clinical effectiveness and cost effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women

Thank you for sending us the Assessment Report for the above Technology Appraisal, for which we are a commentator.

We note that this has an Addendum "The clinical effectiveness and cost effectiveness of technologies for the primary prevention of osteoporotic fragility fractures in post menopausal women," for which we are a consultee. The aforementioned Assessment Report also contains the methodology for the Addendum and some work on screening.

In order to avoid confusion, and hopefully to ensure that our input is appropriately directed, we have therefore separated our response under headings relevant to the various sections of this report as follows:-

1) Comments on the Assessment Report for Strontium Ranelate (Primary and Secondary Prevention)
2) Comments on the Primary prevention Addendum (including comments on screening strategy)
3) Comments on the Primary prevention Addendum relating to Secondary Prevention.

Unfortunately combining these documents in this manner has resulted in some lack of clarity – for example it is not clear how the work on primary prevention screening (section 4.2) of the strontium ranelate TAR relates to treatment with medications other than strontium and alendronate.

Finally we welcome the use of the WHO algorithm, but its submission as "Academic in confidence" has not enabled us to comment on its content, as all data has been blacked out.

Hopefully our responses to the document are clear – if not, please let us know.

Yours sincerely

Dr Debbie Stephenson, MBBS MRCPsych FFPM
Medical Advisor and Head of HTA Strategy

General Comments

1 - Comments from Eli Lilly and Company on the Assessment Report for Strontium Ranelate (Primary and Secondary Prevention)

The clinical effectiveness of strontium ranelate has not been compared with other technologies previously assessed by NICE (other than alendronate). This results in difficulty for the Appraisal Committee in positioning the use of strontium ranelate in the clinical setting.

We suggest that, based on pharmacological, chemical and economic grounds strontium is an antiresorptive which should be used second line to bisphosphonates (in patients unable to tolerate bisphosphonates) in patients without severe osteoporosis. (The second line position in more severe patients being teriparatide).

a) Primary Prevention

In support of our general comments above, we note that on page 106 of the Assessment report it states

"Thus to maximise the net benefit it appears that strontium ranelate should be reserved for women unable or unwilling to take more cost-effective interventions."

In addition on page 110 of the report it states:-

"The efficacy of strontium ranelate at the hip is uncertain, and for all women with osteoporosis, is non significant. Analysis has however, been carried out assuming a beneficial effect at the hip assuming the mean relative risk from the trials. Sub-group analyses has been undertaken by the manufacturer of the intervention to show a significant, and more efficacious effect in older women (aged 74 years and upwards).
On the advice of the GDG, all interventions for the prevention of osteoporotic fractures are assumed to have the same efficacy regardless of the T-Score, prior fracture history, or age of the woman. If strontium ranelate does have a differential effect based on the characteristics (and absolute fracture risk) of a woman this needs to be proven."

b) Secondary Prevention

Strontium ranelate has not been compared clinically with other available therapies (eg. raloxifene, teriparatide). The TAR points to a place in therapy similar to that of bisphosphonates but with reduced cost effectiveness.

The guidance on strontium ranelate needs to be consistent with existing Guidance number 87. New medicines being reviewed after Guidance is published on comparators should not gain any undue advantage. Based on available clinical and economic evidence, it appears that the appropriate use of strontium ranelate is as an alternative antiresorptive treatment for women unable to tolerate a bisphosphonate.

However the Guidance in number 87 should stand, and teriparatide should remain the only option in women with an inadequate response to bisphosphonates who meet the defined severity criteria.

2 - Comments from Eli Lilly and Company on the Primary prevention Addendum (including comments on screening strategy)

General Comments

The methodology for this addendum and information on the WHO algorithm were unfortunately contained in the Assessment Report for strontium ranelate (TAR). We do not believe that this approach was helpful.

Screening

The cost of screening women (on which we previously commented in our letter of 4th April 2005) was also part of the strontium ranelate TAR. It is not clear from this document how the cost effectiveness of screening and treatment applies to raloxifene or other osteoporosis medications other than strontium ranelate or alendronate.

Primary Prevention

The important contribution of this addendum is that it confirms previous work indicating that raloxifene is the only cost effective medication in younger women with less severe osteoporosis when the breast cancer benefit is taken into consideration.

We would therefore once again urge NICE to reconsider its attitude to the breast cancer benefit of raloxifene as discounting it will deny many women a cost effective treatment for their osteoporosis.

3 - Comments from Eli Lilly and Company on the Primary prevention Addendum (relating to Secondary Prevention)

Rather than update the Guidance number 87, we would encourage NICE to take into account the findings in the addendum in relation to secondary prevention within the context of the forthcoming Guideline on the management of osteoporosis.

For teriparatide, we note that this section is consistent with the previous NICE Guidance on secondary prevention No. 87. However, in addition (and as previously presented by Eli Lilly at Appeal) we note that teriparatide is cost effective in both younger women with higher level of risk factors (tables 13-15, p22-23) and in older women with lower risk factors (table 19, p25). Now that the proper analysis of cost effectiveness thresholds has been completed, we hope that the Guideline will reflect this in defining more clinically relevant patient groups suitable for teriparatide.

Raloxifene is again shown, in conjunction with the breast cancer benefit to still be the most cost-effective option in secondary prevention in younger women with lower risk factors. In drafting the Guideline, we would once again urge NICE to reconsider its attitude to the breast cancer benefit of raloxifene as discounting it will deny many women a cost effective treatment for their osteoporosis.