Raloxifene Treatment for Osteoporosis – Comments on Company Submission

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Background

This document provides comments on the company submission for the use of Raloxifene for the treatment of osteoporosis, and in particular the interpretation (and validity there of) of the publicly available evidence regarding the effect of raloxifene on the risk of breast cancer and cardiovascular events.

Breast Cancer

Results of the MORE Study indicate a RR of 0.24 [95% CI: 0.13 to 0.44] at median of 40 months (Cummings *et al*, 1999) and RR of 0.38 [95% CI: 0.24 to 0.58] at median 48 months for all cancers (invasive and non-invasive) (Cauley *et al*, 2001). Clearly further follow-up is required to verify these findings and reduce the level of uncertainty further, and is currently being undertaken as part of the CORE study.

Whilst the company submission reports that with respect to adverse events, e.g. breast pain and enlargement, it would appear that there is not an increase in risk for raloxifene compared to ERT or HRT, the MORE study reports the results of raloxifene compared to placebo for which there was not a statistically significant difference ($P>0.7$) (Cauley *et al*, 2001).

There are a number of reasons to believe why the risk of breast cancer might be related (inversely) to cardiovascular risk, e.g. socioeconomic status. If an economic decision model considers a high risk cardiovascular population, then ideally a subgroup analysis of the MORE study (and in the future the CORE study) restricted to high risk cardiovascular patients should be undertaken to obtain an estimate of the risk reduction in terms of breast cancer for that specific population.

Cardiovascular Disease

The effect of raloxifene on any cardiovascular event (fatal and non-fatal) for the whole cohort of women in the MORE study was 0.86 [95% CI: 0.64 to 1.15] for a dose of 60 mg/d and 0.98 [95% CI: 0.74 to 1.30] for 120 mg/d Barrett-Connor *et al*, 2002). Consideration of separate fatal and non-fatal cardiovascular events (coronary/cerebrovascular) did not however find a statistically significant benefit for raloxifene.

However, considering a high risk population the effect of raloxifene on any cardiovascular event (fatal and non-fatal) was 0.60 [95% CI: 0.38 to 0.95] for a dose of 60 mg/d and 0.60 [95% CI: 0.38 to 0.95] for 120 mg/d Barrett-Connor *et al*, 2002). Consideration of separate fatal and non-fatal cardiovascular events (coronary/cerebrovascular) did not however find a statistically significant benefit for raloxifene, except when considering all strokes, RR 0.38 [95% CI: 0.15 to 0.94].

Definition of 'high risk' is based upon a previously published risk scoring method developed for the RUTH study (Mosca *et al*, 2001) and applied retrospectively to the MORE population. Whilst there is evidence that there is an underlying risk – effect relationship (Barrett-Connor *et al*, 2002:Figure 4) the risk scoring system is nevertheless crude in the sense that 'high risk' is defined as score of 4 or more and such a score could be achieved in a variety of different ways, and therefore the 'high risk' population reported in the company submission may in fact be quite heterogeneous clinically. Whilst the results of any decision model based on such analyses may not in fact be particularly sensitive to the definition of 'high risk' it may nevertheless be difficult to translate the findings into clinical practice. An alternative approach would be to define a specific and clinically homogeneous population and to estimate the benefit of raloxifene treatment for this population and the resulting estimate of cost-effectiveness.

In the company submission a sensitivity analysis of the decision model uses a relative risk reduction for all cardiovascular events of 20%. This is based upon the effect of raloxifene in the *whole* MORE study population in terms of its effect on serum lipids and uses a previously published meta-analysis regarding the relationship between serum lipid levels and cardiovascular events (Law *et al*, 1994) to derive the subsequent effect on cardiovascular events. Whilst we are uncertain as to the specific manner in which uncertainty is handled in the company model, such a derivation introduces two separate sources of uncertainty – uncertainty surrounding the reduction in serum lipids observed in the MORE study and uncertainty regarding the relationship between serum lipids and cardiovascular events. Clearly, in any probabilistic decision model both sources of uncertainty should be properly accounted for.

Other Outcomes & Considerations

It should be noted that Cauley *et al* (2001) [Table 5] also report a statistically significant increase in the risk of thromboembolic disease (DVT & PE) associated with the use of raloxifene. For placebo, 60 mg/d and 120 mg/d the events per 1,000 woman years were 1.44, 3.32 and 3.63 respectively. Based on the observed numbers of events reported by Cauley *et al* (2001) [Table 5] (12/2576 in the placebo group, 28/2557 for 60 mg/d & 31/2572 for 120 mg/d) a RR of 2.35 [95% CI: 1.20 to 4.62, P=0.01] is obtained for 60 mg/d compared to placebo, whilst for 120 mg/d compared to placebo a RR of 2.59 [95% CI: 1.33 to 5.03, P=0.004] is obtained. For the two doses of raloxifene combined compared to placebo a RR of 2.47 [95% CI: 1.33 to 4.59, P=0.003] is obtained. Mortality at 3 months in patients suffering a PE has been reported as 15.8% (Goldhaber *et al*, 1999). Clearly such an increase in the risk of a potentially serious adverse event needs to be considered when constructing an economic decision model.

The MORE study specifically considers an *osteoporotic population* and therefore generalisability of the results to either a more general population or in fact a different specific population, e.g. high cardiovascular risk *per se* or high breast cancer risk, should be undertaken with extreme caution and ideally await the results of studies currently underway (STAR & RUTH), or at the very least be updated in the light of these results.

References

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