National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Statement of Reasons

Introduction

1. This statement is provided to inform Servier of the concerns of NICE, at the time of the appraisal of alendronate, risedronate, etidronate, raloxifene, strontium ranelate and teriparatide for the primary/ secondary prevention of osteoporotic fractures, on use of the post hoc subgroup analysis of the TROPOS study, submitted to the European Medicines Agency (EMA), in the context of making recommendations about the clinical and cost effectiveness of strontium ranelate.

2. This document is to enable Servier to consider the content of a submission to NICE on the use of the subgroup analysis in determining the relative effectiveness of strontium ranelate for the treatment of women with osteoporosis.

Areas

Subgroup analyses

3 NICE believes that the results for the subgroup are from a non-prespecified, retrospective subgroup analysis. Servier has indicated that the EMA requested this subgroup analysis. The EPAR states that EMA requested data for a subgroup of women with prior fracture and a T score -2.5. Servier provided a subgroup analysis of women with osteoporosis over the age of 74. NICE wishes to understand the position of Servier with regard to the general scientific rationale for the selection of this particular group by Servier. The communication between Servier and EMA that resulted in EMA's acceptance of the subgroup analysis has not been seen by NICE. NICE are also unclear about whether Servier performed other subgroup analyses of the TROPOS study in addition to the analysis finally presented. The general reasons for caution in relying on non-prespecified subgroup analyses are well reported in the literature and are not repeated here.

Information required

4 NICE wishes to see evidence demonstrating whether or not multiple explorations of the TROPOS data have occurred in order to identify the subgroup finally presented to EMA.

5 NICE wishes to see a full account of dealings with the EMA on the question of subgroup analysis in the TROPOS study including, but not limited to, all original documentation bearing on this question; all communication relating to the subgroup analysis; the ‘day 120’ questions and responses and ‘day 180’ meeting notes, questions and responses.

Justification for the particular subgroup chosen

6 Servier has indicated that the subgroup modelled represents the "high risk" group of patients. NICE is unaware of the justification for this claim. In particular, as presently informed, it regards the introduction of the particular age cut-off as the definition of a clinically plausible high risk group as unjustified without pre-specification. NICE is fully aware that age is a clear risk factor for osteoporotic fracture and that this increase in risk is gradual. NICE is unaware of a justification for a cut-off at age 74, as opposed to any other age, as the defining feature of a high risk category. Furthermore, NICE is unaware of data that suggest that the relative risk reduction achieved through any treatment changes with age in a post-menopausal osteoporotic population and therefore unaware of a biologically plausible reason to support a finding that Strontium Ranelate is more effective in the TROPOS subgroup population compared to the overall TROPOS population.

Information required

7 NICE wishes to see, by reference to contemporaneous documentation at the time of the submission of the subgroup to the EMA, the justification for the age-cut off at 74.

8 NICE wishes to see evidence providing a biological basis for the claim that the subgroup experiences greater benefit than the trial population overall. Please note that NICE does not regard the fact that the subgroup was accepted by the EMA as determinative.

9 Depending on whether or not more than this high risk subgroup analysis has been performed on the TROPOS dataset (see point 4), NICE wishes Servier either to confirm that the subgroup presented to the EMA was the only subgroup analysis performed on the TROPOS dataset, or to provide full details of all exploratory subgroup analyses of the TROPOS dataset and the detailed results of these analyses. Subgroup analyses should be presented demonstrating that the appropriate statistical techniques have been used to correct for multiple sub-group analyses.

Extrapolation from the subgroup to the patient population at large

10 If the subgroup analysis is considered robust, it is still necessary to establish whether the result derived from the subgroup can be applied across the whole TROPOS population. NICE's starting point is that where it has robust trial data for a complete population it will use that data. In so far as the Court of Appeal may have suggested that NICE must first conclude that the subgroup is unreliable before preferring the overall trial data, NICE respectfully disagrees on what is a pure issue of scientific method. The default position is to use the complete and properly randomised data set, not a selection from it. NICE does not understand why Servier argues that this scientific position should not be taken.

11 If the subgroup contains a population who experience an above average benefit from treatment, it follows unavoidably that the remaining 'subgroup' must experience a below average benefit from treatment. This appears to be highlighted in Servier's description of the subgroup as "high risk". By using that description it follows that Servier regards that the remaining patients are at "low(er) risk". It therefore follows that, as the benefit of treatment is a percentage reduction in events (fractures), the number of fractures prevented (i.e. the benefit), must be lower in the lower risk group.

12 If the overall TROPOS data is not to be used it must be because it is in some way unreliable.

Information required

13 NICE wishes Servier to outline the scientific and statistical rationale for not using the efficacy data derived from the whole TROPOS clinical trial population in making recommendations that apply to this population.

14 NICE wishes Servier to present a statistical rationale for the use of a data set derived from a subgroup in a trial in preference to the use of the whole trial data set. In doing so, NICE wishes Servier to explain, from a statistical perspective, why the use of statistical analysis derived from the whole TROPOS study is not reliable or not robust.

15 NICE would like Servier to provide statistical analyses, including central estimates of effect with confidence intervals, from the TROPOS population after the 'subgroup' dataset is removed from the overall TROPOS dataset (i.e. all women not in the subgroup) and for the population of women with a T score of-2.5 or below under the age of 74 (i.e. all women with osteoporosis under the age of 74).

Decisions made by another authority

16 The EMA is a body with a different remit and different processes. NICE does not regard the fact that this subgroup analysis may have been relied on, to any degree, by the EMA as an answer in itself to any of NICE's own enquiries

above. The EMA may be in error or simply have reached a different conclusion as an exercise of expert judgement.

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May 2010