Amended Appeal Notice against two final appraisal determinations on the treatment of osteoporosis distributed on 26 June 2007 submitted by Servier Laboratories Ltd

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Introduction

Please note that this submission amends the initial Appeal submission against the two published appraisal determinations ("FADs") submitted by Servier Laboratories Ltd on 9th July 2007 , at the request of the Chairman of the Appeal Panel in correspondence dated 15 August 2007.

Following receipt of the letter detailing the preliminary assessment from the Appeal Panel , the Applicant has renumbered this Appeal Document for ease of reading. The Applicant has also developed arguments where clarification was requested. It should be noted that the Applicant does not agree with all the points of the preliminary assessment and accordingly has maintained those points where there is disagreement.

Appeal

On 26 June 2007, NICE ("the Institute") published two final appraisal determinations ("FADs") on the treatment of osteoporosis: (i) "*Alendronate, etidronate, risedronate and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women*" ("FAD1") and (ii) "*Alendronate, etidronate, risedronate, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women"* ("FAD2"). Despite being a leading and first in its class product, for the primary and secondary prevention of osteoporosis due to its unique evidence that it both stimulates bone formation and reduces bone resorption, as recognised by the EMEA (the European Medicines Agency), strontium ranelate was not recommended in either of the two FADs for the treatment of osteoporosis.

By this submission, Servier Laboratories Ltd ("the Applicant") as the marketing authorisation holder for strontium ranelate (Protelos®) is appealing against the two FADs as published. Namely: (1) that the Institute has acted unfairly and not in accordance with their published procedures; (2) that the FADs are perverse in light of the evidence submitted; and (3) and that the Institute has exceeded its powers.

The Applicant asks the Appeal Committee to direct that the FADs are reassessed taking into account all evidence submitted and taking into account all the patient populations without discrimination, that the Institute uses consistent decision making and appropriate economic models with full transparency and that the Institute act in accordance with the published procedures and within the remit of the Institute's powers.

Executive Summary

The Applicant contends that:

1. <u>Appeal on Ground 1:</u> The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process.

1.1. The Appraisal Committee has demonstrated inconsistent decision making in standards applied within this appraisal in the application of the hierarchy of evidence

By acting inconsistently in their use of the hierarchy of evidence, the Appraisal Committee has ignored better quality evidence in favour of lesser quality evidence. This was done when the Committee rejected evidence of hip fracture prevention by strontium ranelate demonstrated in a post-hoc sub-group analysis (Class 1^{+}), an analysis requested and endorsed by the EMEA, whilst it accepted evidence for hip fracture prevention by etidronate demonstrated in a post-marketing observational study (Class 2^{-}). As a result, there was a considerable disadvantage for strontium ranelate in the economic analysis. This approach is discriminatory and unfair and resulted in the Institute erroneously concluding that strontium ranelate was not cost effective.

1.2 The Appraisal Committee has changed the scope of the appraisal without direction from the Department of Health and without consultation with stakeholders

Despite clearly laid out procedures for the determination of the scope of an appraisal, the Institute has acted in breach of these procedures. The agreed scope for this appraisal originally included the possibility to recommend treatments for patients who are contraindicated or who could not tolerate first line therapy. However, at a very late stage in the appraisal, the Appraisal Committee itself amended the scope, to <u>only</u> consider drugs for the initiation of therapy for postmenopausal osteoporosis.

The Appraisal Committee decided to move the decision on second line use from the status of "*guidance*" that it is mandatory for the NHS to implement (the technology appraisal) to the status of "*a clinical guideline*", which it is not mandatory for the NHS to implement (the importance of this distinction is underlined by Justice Dobbs in Eisai v. NICE, para. 99 (10/08/2007)). As a result, evidence exists that guidance is implemented, as it imposes a duty on the PCTs (para. 99 of the Eisai Case) while guidelines are very often not implemented. The result of this decision is a substantive loss of access for patients to alternative funded medicine (i.e. strontium ranelate) both now and in the future. This situation is further exacerbated by the fact that the clinical guideline is not yet prepared therefore resulting in the needs of an important part of the patient population not being taken into account by the Appraisal Committee. The issues set out in this point also raises issues of abuse of power further addressed in Ground 3.

1.3. The Appraisal Committee has demonstrated internally inconsistent decision making with the generalisation of relative risk data generated in low risk patients and extrapolated to all patients under consideration.

By failing to consider subgroup populations, the Institute has acted unfairly and in violation of published procedures. The result of this is that there was a considerable disadvantage for strontium ranelate in the economic analysis.

The internal inconsistency relates to the way in which data were synthesised to estimate the efficacy that informed the base case for vertebral fracture compared to the way it was done for hip fractures. In the case of vertebral fractures, a high risk sub-group was allowed to be the basis for informing the generalised estimate of treatment effect. This sub-group is defined as patients with a previous fracture. However, when estimating the efficacy of strontium ranelate in hip fracture, the Appraisal Committee did not admit the use of data drawn from a high risk sub-group and instead insisted on the use of data which included patients of a very low fracture risk (indeed those without osteoporosis at all). The power to demonstrate a treatment effect in this larger group was much less. This decision was made despite the opposite conclusion being drawn by the EMEA, who granted a hip fracture license on the basis of the high-risk sub-group data. Another health technology appraisal agency, the Scottish Medicines Consortium, has also assessed strontium ranelate and has endorsed the hip fracture data that is the basis for the hip fracture license.

This resulted in the Institute erroneously concluding that strontium ranelate was not cost effective and subsequently it was not recommended in the FADs due to the failure of the Institute to act fairly in this appraisal.

1.4. The Appraisal Committee has failed to address new evidence

By failing to consider material new evidence that was submitted on the increase in fracture risk associated with the use of acid suppressing agents during the appraisal process, the Institute has acted unfairly.

The Institute has not acted in accordance with published procedure (i.e. sections 1.2.5 and 1.2.8 of the Guide to the Technology Appraisal Process) as the evidence impacts on quality of life and the probable effects on mortality were not considered. The Institute has acted unfairly by ignoring material evidence which led it to erroneously conclude that strontium ranelate should not be recommended while the cost effectiveness assessment was based on incomplete data. From the patient's point of view, it resulted in a lesser quality of life for some categories of patients.

Therefore, by not adhering to the guidance provided in the Social Value Judgements the Institute has acted unfairly, as there is an expectation from the Appraisee that the Appraisal Committee will follow the guidance issued by an eminent former member of NICE.

1.5. The Appraisal Committee has failed to provide the economic model on which the appraisal was based

The Institute has failed to act in accordance with the principle of transparency during the appraisal process by not publishing the economic model. In addition, the Institute has failed to act in accordance with its published procedure by providing insufficient details of the economic model when requested. It was therefore impossible for

consultees to challenge the assumptions made and to supply data that might have assisted with the discussions on the assumptions. As a consequence of this, the resulting economic analysis was overly negative towards treatment with strontium ranelate.

Our case can be distinguished from the recent Eisai v NICE Case. The Appellant did not have access to the nature of the assumptions which are "at the heart of the Model" (para 61 of the Judgment) and therefore the Appellant had no means of criticising the Model, its approach and the system. The Appellant was clearly denied access to significant information and deprived of the opportunity to make an intelligent response.

The High Court judgment in Eisai records that consultees were presented with a read-only model, which, although not fully executable, was at least partly executable. The judgement reported that the consultees were able to view the assumptions underlying the model and that they were only unable to undertake sensitivity analysis. This was not the case with the current appraisal. Consultees were presented with a 'read-only version', which was essentially a series of blacked out inputs and results spreadsheets and this did not provide sufficient information to challenge the economic assessment made by the Appraisal Committee. The spreadsheets are not informative about the underlying assumptions and structure of the model. Therefore, they cannot be considered a "model" in any respect, read-only or otherwise.

The consequence of this is that substantial debate about the assumptions underlying the model was not possible. Among these was the assumption about the *fall time* used in the model, which was not considered in the sensitivity analysis and, if it had been, would have changed the perception of the cost effectiveness of all drugs.

In summary, the Institute has acted unfairly and not in accordance with published procedures by providing the economic model in a substantially redacted form. Therefore, preventing the Applicant from instructing its own experts to check the accuracy of the model used and the overall quality of such a model. Further, the Institute has failed to act in accordance with the principle of transparency.

1.6. The Appraisal Committee has failed to act in accordance with the published procedure on encouraging innovation

The Institute has failed to act in accordance with the published procedure on encouraging innovation by not recommending strontium ranelate as a new innovative class of therapy, in a market dominated by bisphosphonate therapy. The result of this failure to provide access to a diversity of treatment is to leave at risk patients exposed to the risk associated with the bisphosphonate safety profile.

2. <u>Appeal on Ground 2:</u> The Appraisal Committee has drawn a conclusion that is perverse in the light of the evidence submitted

2.1. The Appraisal Committee has failed to adhere to proper processes for accounting for important scientific evidence

Substantial evidence on the increase in fracture risk associated with acid suppressant use was submitted on multiple occasions during the appraisal as part of official consultations. **[CONFIDENTIAL INFORMATION REMOVED]** Whilst aware of

the substantial evidence of the safety risk associated with acid suppression in patients at risk of a fracture, the Appraisal Committee failed to direct the Decision Support Unit ("DSU") to consider the increase in fracture risk associated with the use of acid suppressing agents. Furthermore, the Appraisal Committee at no time directly addressed the points being made, despite the clarity in which they were made and never justified their exclusion from consideration.

By failing to recognise the exceptional circumstances applied such that further analysis of the new data was necessary, the Appraisal Committee has been perverse.

2.2. By ignoring a critical piece of evidence, the Appraisal Committee has made a recommendation that will result in increased expenditure and increased fractures compared to a cost effective alternative.

The Appraisal Committee was made aware on a number of occasions about the risk associated with acid suppression for patients at risk of fracture. Comments were made on multiple occasions during official consultation phases and, later, during the preparation of the FAD that convincing evidence exists that because bisphosphonates increase the risk of acid suppressant use, recommendations should be made that minimise the use of bisphosphonates in patients at risk of or taking an acid-suppressing agent.

The Appraisal Committee chose, without justification, to ignore this evidence. The result is that physicians are directed by the FADs towards prescribing a medicinal product that will ultimately cause dyspepsia in a percentage of cases with the treatment prescribed to counteract this dyspepsia increasing fracture risk. By failing to take this scientific evidence into consideration, the Institute has acted against the principle of nonmaleficence and recommended a product that could inflict harm on patients, in addition to costing the NHS resources, for no benefit. This decision is clearly perverse in the light of the evidence.

2.3. The Appraisal Committee has demonstrated internally inconsistent decision making with the generalisation of relative risk data generated in low risk patients and extrapolated to all patients under consideration

There is a lack of internal consistency in the way in which data were synthesised by the Appraisal Committee to estimate the efficacy data that informed the base case for vertebral fracture prevention compared to the way the Appraisal Committee selected the data for hip fracture prevention by for strontium ranelate as discussed in section 1.3 above.

In the case of vertebral fractures, a high-risk sub-group was selected as the basis for informing the generalised estimate of treatment effect. This sub-group is defined as patients with a previous fracture. However, when estimating the efficacy of strontium ranelate in hip fracture, the committee did not admit the use of data drawn from a high risk sub-group and instead insisted on the use of data which included patients of a very low fracture risk (which included patients with no osteoporosis at all). The power to demonstrate a treatment effect in this larger group was insufficient and, consequentially, the confidence interval around the result is much wider. The decision by the Appraisal Committee was made despite the opposite conclusion being drawn by the EMEA, who granted a hip fracture license on the basis of the high-risk sub-group data.

By the extrapolation of data from low risk patients to all patients, the Appraisal Committee has reached an erroneous and perverse conclusion on the measure of effectiveness of the medicinal products reviewed in the FADs. As a consequence, the Institute has incorrectly concluded that strontium ranelate is not as effective a treatment when compared with bisphosphonates.

3. <u>Appeal on Ground 3</u>: The Institute has exceeded its powers

3.1. The Appraisal Committee has amended the scope of the appraisal without direction from the Department of Health and without consultation with stakeholders

The Institute has exceeded its powers by unilaterally amending the scope of the appraisal. The result of this is that the FADs only considered drugs for the initiation of therapy for postmenopausal osteoporosis. The consequence of this decision is that patients have been recommended a product with detrimental side effects for some patients, to the exclusion of other choices of treatment. Strontium ranelate is not associated with these side effects and is cost effective, compared to no treatment.

3.2. The Institute has exceeded its powers in taking actions that are not in accordance with the Human Rights Act.

The approach of the Institute has affected the quality of life of patients and discriminates against patient populations in a manner, which constitutes a violation of both Articles 8 and 14 of the Convention for the Protection of Human Rights and Fundamental Freedoms (ECHR) (as amended)[1] (as incorporated in the UK by the Human Rights Act 1998).).

In particular, the Appraisal Committee deliberately excluded women who do not respond to a treatment with alendronate or cannot tolerate it or for whom alendronate is contra-indicated from the right to obtain funded medication from the NHS. The appraisals are clearly discriminatory on its face as it discriminates these categories of patients from the rest of the relevant patient population, which will benefit from funded medicine.

In addition, the appraisal discriminates on the grounds of age as a woman will only be entitled or not to a funded treatment by reference to her age. This is contrary to Article 14, read together with Article 8, as there is no objective and reasonable justification to this discrimination.

[1] Article 8: Right to respect for private and family life which reads as follows:
"*1. Everyone has the right to respect for his private and family life, his home and his correspondence.*
2. There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others."
Article 14 : Prohibition of discrimination which reads as follows:
"The enjoyment of the rights and freedoms set forth in this Convention shall be secured without discrimination on any ground such as sex, race, colour, language, religion, political or other opinion, national or social origin, association with a national minority, property, birth or other status."

All these points constitute a violation of Article 8 and 14 of the ECHR

1. Appeal on Ground 1 The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process

1.1 The Appraisal Committee has demonstrated inconsistent decision making in standards applied within this appraisal in their application of the hierarchy of evidence

The Institute has deviated from the agreed hierarchy of evidence and has ignored evidence from a higher level of hierarchy in favour of evidence from a lower level of hierarchy.

1.1.1 Background

The Institute has published a table depicting the hierarchy of evidence that is to be used in the development of clinical guidelines and technology appraisals. This is represented in the table below:

Level of evidence	Type of evidence
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2^{++}	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2^{+}	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2^{-}	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus

Despite this hierarchy of evidence, the Institute took account of a lower level of evidence (namely, the observational study data for etidronate (2-) (see section 1.1.2)) in making its appraisal determination and ignored a higher level of evidence (namely, a post hoc sub group analysis from a randomised, controlled, clinical trial for strontium ranelate (1+) (see section 3.1 which discussed the TROPOS study)) that had

been presented. The Institute also acted with internal inconsistency and this is explained further below.

1.1.2 Internal inconsistency

The Appraisal Committee has stated that the decision to reject the analysis of hip fracture efficacy, which was the basis for the licence, was that the subgroup analysis was not pre specified[2]. Assessing the sub-group analysis using the hierarchy supplied above, the evidence stands at Class 1^+. However, the Appraisal Committee had previously endorsed the use of the hip fracture data demonstrated by etidronate in an observational study[3], which could certainly be described as a Class 2^- study.

Data to support etidronate is clearly lower on the hierarchy of evidence than that supplied to support strontium ranelate for the prevention of hip fracture.

In summary, the inconsistent application of a scientific principle has resulted in a considerable disadvantage for strontium ranelate in the economic analysis and a distorted picture of cost effectiveness. The decision is perverse in the light of the evidence submitted of a better quality hierarchically. Further, this approach is not in accordance with section 3.2.3.1 of the Guide to the Methods of Technology Appraisal which provides that:

> " *In the absence of valid RCT evidence, evidence from the highest available level of study design will be considered with reference to the inherent limitations of the specific design."* (emphasis added)

Further, section 3.2.1.3 of the Guide to the Methods of Technology Appraisal provides that good quality observational studies may be needed to supplement the RCT data but not to replace it:

"Studies lower in the hierarchy are more prone to bias including publication, retrieval, selection, performance, measurement and attrition biases. However, it is important to recognise that (even as regards the analysis of relative treatment effects) RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore, good-quality observational studies will often be needed to supplement the RCT data. In addition, the value of evidence from anywhere in the hierarchy will depend on its quality and relevance". (emphasis added)

As such, the Institute has failed to act in accordance with published procedure.

1.1.3 Consequences for the Evaluation of Strontium Ranelate

The inconsistent application of a scientific principle has resulted in a considerable disadvantage for strontium ranelate in the economic analysis and a distorted picture of cost effectiveness.

[2] The two ACDs for primary and secondary prevention of fragility fractures in PMO dated September 2006

[3] The two ACDs for primary and secondary prevention of fragility fractures in PMO dated September 2006

1.2 The Appraisal Committee has changed the scope of the appraisal without direction from the Department of Health and without consultation with stakeholders

The Institute has acted unfairly and violated its published procedures by its failure to follow the agreed procedure for establishing the scope of an appraisal, by subsequent amendments that were not agreed with the appropriate parties.

According to sections 3.1-3.5 of the Guide to the Technology Appraisal Process, the scope of an appraisal process is produced in consultation with consultees and commentators, the Assessment Group, the Department of Health, the Welsh Assembly Government and other interested parties. Once the final remit has been produced by the Department of Health and Welsh Assembly Government, the final scope and matrix of consultees and commentators are produced by the Institute. The Ministers then make a final decision on referral to the Institute to begin the appraisal process:

> ***"3.1 Provisional list of technologies for referral***
>
> *3.1.1 Once a provisional list of appraisals selected for further consultation is decided by Ministers, and before a formal referral, the Institute works with the Department of Health and the Welsh Assembly Government to develop a scope for the appraisal. The steps involved in developing the scope begin before the technology is formally referred to NICE for appraisal. At this stage, there is no guarantee that the technology will be referred.*
>
> *3.1.2 When Ministers have provisionally decided on the list of technologies for appraisal (known as a 'wave') that may make up the referral to NICE, the Institute undertakes the following tasks:*
>
> - *develops a draft scope*
> - *identifies organisations that may wish to participate in the appraisal*
> - *consults (in conjunction with the Department of Health and Welsh Assembly Government) on the draft scope for the appraisal*
> - *holds a scoping workshop.*
>
> *3.1.3 The steps involved in developing scope are shown in Figure 1 (page 5).*
>
> ***3.2 Developing the draft scope***
>
> *3.2.1 During topic selection, the Department of Health and the Welsh Assembly Government provide the Institute with a draft remit for the appraisal. The Institute then undertakes a draft scoping process, which sets the provisional parameters of the appraisal and identifies the potential questions that would need to be asked about each technology. The scope will steer and focus the appraisal if the technology is formally referred to the Institute.*
>
> *3.2.2 The first step in the scoping process is identification of information relating to the technology and preparation of a draft scope. The Institute's information specialists, working with the Institute's Technical Leads, undertake this task, which includes conducting a literature search, speaking with clinical specialists and contacting the manufacturer or sponsor of the technology.*

3.2.3 The draft scope of an appraisal aims to define a number of elements, including:

- *the clinical problem and the population(s) and any relevant subgroups for whom treatment with or use of the technology is being appraised*
- *the technology and the setting for its use*
- *the relevant comparator technologies (and their treatment settings) – usually, the relevant comparators are the treatment(s) used in current clinical practice in the NHS to manage the disease/condition, which may include no treatment (for further details, see the Guide to the Methods of Technology Appraisal)*
- *the principal health outcome measures appropriate for analysis*
- *the measures of costs to be assessed*
- *the time horizon over which the benefits and costs will be considered*
- *special considerations and issues that are likely to affect the appraisal.*

3.2.4 For further information on scoping the appraisal, refer to the Guide to the Methods of Technology Appraisal.

3.2.5 Unless the Department of Health or the Welsh Assembly Government indicates otherwise, appraisals do not normally include consideration of the use of a technology for indications for which regulatory approval has not been granted in the UK.

3.2.6 Further refinement of the draft scope may be undertaken at the request of Ministers.

3.2.7 Ministers review the proposals of the ACTS together with the corresponding draft remits and scopes and decide on the technologies that they are minded to refer to the Institute for appraisal.

3.3 Consultation

3.3.1 The next step is a consultation stage on the scope. This process is initiated once Ministers are minded to refer a 'wave' of topics to the Institute. The Institute then identifies the organisations that might be interested in the appraisal. These fall into two groups: consultees and commentators (see Box 4.1, page 11). The Institute sends the draft remit and draft scope to provisional consultees and commentators, and to the Assessment Group, together with the list of provisional consultees and commentators, for comment. Comments should be submitted to the Institute within 20 working days. The draft scope is also posted on the Institute's website for information.

3.3.2 Manufacturers and sponsors are asked to include in their comments on the draft scope any information regarding pending licence applications for their technologies. This must include the timeframe within which regulatory approval is anticipated.

3.4 The scoping workshop

3.4.1 After provisional consultees and commentators have submitted their comments on the draft remit and draft scope, a meeting is held to which the Assessment Group, all provisional consultees and commentators, the Department of

Health, the Welsh Assembly Government, and other interested parties are invited. A senior member of the appraisals team or one of the Institute's Executive Directors chairs the scoping workshop.

3.4.2 The scoping workshop is held approximately 8 weeks after the initiation of the consultation period. The aims of the meeting are to:

- *ensure that the scope is appropriately defined*
- *discuss the issues raised by consultees and commentators during consultation on the draft scope*
- *identify important data pertinent to the appraisal*
- *ensure that relevant issues are highlighted to the Assessment Group to inform the development of their protocol.*

3.4.3 It is important that sufficient clinical expertise is fed into the development of the scope.

3.4.4 Manufacturers are encouraged to provide preliminary details of the evidence that they would submit to an appraisal.

3.5 Final scope

3.51 Taking into account comments received on the draft scope and the discussions at the scoping workshop, the Department of Health and the Welsh Assembly Government prepare a final remit and the Institute produces a final scope and a final matrix of consultees and commentators for the appraisal, in anticipation of receiving a formal referral from the Secretary of State for Health and the Welsh Assembly Government.

3.5.2 Discussions at the scoping workshop also assist the Assessment Group in developing its protocol for the technology assessment. For further information, see the Institute's Guide to the Methods of Technology Appraisal.

3.5.3 The final scope is submitted to Ministers for a decision on whether the technology appraisal is suitable for formal referral to the Institute. Occasionally, as a result of the information gathered during scoping, the Department of Health and the Welsh Assembly Government may decide not to refer a technology or group of technologies for which a draft remit and scope have been developed and consulted upon.

3.5.4 If Ministers decide that the technology is suitable for referral, the technology is formally referred to the Institute and, at this point, the Institute begins the appraisal process." (emphasis added)

The agreed scope for this appraisal originally included the possibility to recommend treatments for patients who are contraindicated or who could not tolerate first line therapy. However, at a very late stage in the appraisal, the Appraisal Committee itself amended the scope without consultation, to <u>only</u> consider drugs for the initiation of therapy for postmenopausal osteoporosis.

It only became apparent <u>after</u> the publication of the latest in a series of ACDs that the scope of the appraisal had been amended.

This change was made seemingly without a Department of Health direction and without consultation of any third parties. Amendments to the scope of an appraisal should only be made to the draft scope; not to the final scope. This is a clear violation of the Institute's procedures as outlined above.

The result of this decision is to move the decision on second line use from *guidance* that it is mandatory for the NHS to implement (the technology appraisal) to *a clinical guideline*, which it is not mandatory for the NHS to implement (the importance of this distinction is underlined by Justice Dobbs in Eisai v. NICE, para. 99 (10/08/2007)). The result of this decision is a substantive loss of access for patients to strontium ranelate both now and in the future. Further, the clinical guideline is not yet prepared. Please see in particular paragraphs 1 of FAD1 and FAD2. Therefore, the conclusion is that no alternative medicinal product is available to patients for the initiation of therapy.

In summary, the Institute has acted unilaterally in determining the scope of the appraisal, which is unfair and not in accordance with the agreed procedure. Further, the Institute has exceeded its powers in doing so (please see section 1.1.1).

1.3 The Appraisal Committee has demonstrated internally inconsistent decision making with the generalisation of relative risk data generated in low risk patients and extrapolated to all patients under consideration.

1.3.1 Extrapolation of data from low risk groups

As outlined in section 2.3 below, by failing to accept data from relevant high risk subgroups, the Appraisal Committee has reached an erroneous conclusion as to the measure of effectiveness of the medicinal products reviewed under this appraisal. As such, the Institute has failed to act fairly and in accordance with published procedure as a proper consideration of the data has not been undertaken and the Institute has adopted inconsistent policies. Appraisees are in right to expect that the Appraisal Committee will adopt a consistent manner, which will ensure a fair treatment for all appraisals.

Section 1.2.8 of the Guide to the Technology Appraisal Process provides that the degree of clinical need of the patients with the condition under consideration should be taken into account.

Strontium ranelate has demonstrated a statistically significant reduction in the risk of hip fracture. This effect was demonstrated in a high risk subgroup in a post hoc analysis requested by the CHMP and the EMEA and published in an eminent peer reviewed journal[4]. These data were the basis for the indication for hip fracture prevention that was recognised by licensing bodies in the Summary of Product Characteristics ("SmPCs") and endorsed by the Scottish Medicines Consortium.

[4] This result was published in the TROPOS publication: Journal of Endocrinology & Metabolism, "Strontium Ranelate Reduces the Risk of Nonvertebral Fractures in Post-menopausal Women with Osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) Study", (Volume 90, Number 5, May 2005).

The Appraisal Committee refused to consider the subgroup analysis under the TROPOS trial as an appropriate measure of efficacy and instead chose to consider a far higher (and non significant) relative risk, which came from a much lower risk population without the power to detect the treatment effect.

In summary, the failure to adhere to a consistent policy is unfair and in breach of published procedure as there is an erroneous conclusion on the measure of effectiveness of strontium ranelate. In addition the FADs prepared are perverse in light of the evidence submitted (please see section 2.3).

1.4 The Appraisal Committee has failed to address new evidence

1.4.1 Revision of decisions following new evidence

By failing to address new evidence that was relevant to the appraisal, the Institute has acted unfairly and in violation of published procedure.

Senior decision makers within the Institute have directed the Appraisal Committees to provide the opportunities to reconsider decisions with the statement[5]:

> *"Decisions should be capable of revision when new, or additional, evidence or argument becomes available."*

Despite the presentation of arguments to the Appraisal Committee of the increase in fracture risk associated with the use of acid suppressing agents, the Appraisal Committee failed to adequately respond to the presentation of this new evidence.

Further, according to sections 1.2.5 and 1.2.8 of the Guide to the Technology Appraisal Process, the appraisal process should consider the evidence of the health benefits and the impact on quality of life and the probably effects on mortality and properly assess the degree of clinical need of the patients under consideration:

> *1.2.5 An appraisal considers the evidence of the health benefits and costs of a health technology or technologies. This includes the impact on quality of life (for example, relief of pain and disability), and the probable effects on mortality. It also considers estimates of the associated costs, concentrating particularly on costs to the NHS and Personal Social Services.*
>
> *[ ]*
>
> *1.2.8 In reaching the decision, the Institute and the Appraisal Committee take into account the factors listed in the directions of the Secretary of State for Health and the Welsh Assembly Government, namely:*
>
> - *the broad clinical priorities of the Secretary of State for Health and the Welsh Assembly Government (for example, as set out in National Priorities and Planning Framework 2003-2006 and in National Service Frameworks, or any specific guidance on individual referrals)*
> - *the degree of clinical need of the patients with the condition under consideration*

[5] Social Value Judgements – Guidance for the Institute and its Advisory Committees Rawlins 2005

- *the broad balance of benefits and costs*
- *any guidance from the Secretary of State for Health and the Welsh Assembly Government on the resources likely to be available and on such other matters as they think fit*
- *the effective use of available resources."* (emphasis added)

By the failure to consider the new evidence, the Institute has failed to act in accordance with the published procedure as the impact on quality of life and probable effects on mortality are significantly worsened as the increase in fracture risk associated with the use of acid suppressing agents was not considered.

In summary, the failure to consider the new relevant evidence is unfair, as the Institute has not given proper consideration to the evidence submitted. In addition the FADs prepared are perverse in light of the evidence submitted (please see in Ground 2, section 2.1).

1.5 The Appraisal Committee has failed to provide the economic model on which the appraisal was based

1.5.1 Lack of transparency

The Institute has acted unfairly and in violation of its published procedure by failing to provide the economic model, rather than providing a substantially redacted version.

According to section 4.4.1.9 of the Guide to the Technology Appraisal Process, the Institute offers consultees and commentators, following a request in writing, the opportunity to receive by email a read only version subject to certain conditions, for information only provided. A substantially redacted version of the economic model was received on 1 March 2007 despite a request for full access (see Annex 4). This is a clear contravention of the Institute's procedures as outlined above.

> *4.4.1.9 The Assessment Group may produce an economic model in support of the Assessment Report. If the model does not contain information that was designated as confidential in the submission, the Institute offers consultees and commentators the opportunity to receive by email a read-only version of the model, for information only. Requests for the model must be made in writing, and it is supplied on the basis that the consultee or commentator agrees, in writing, to the following conditions for its use.*
>
> - *The economic model and its contents are confidential and are protected by intellectual property rights, which are owned by the relevant Assessment Group. It cannot be used for any purpose other than to inform the recipient's understanding of the Assessment Report.*
> - *The model must not be re-run with alternative assumptions or inputs.*
> - *The consultees or commentators will not publish the model wholly or in part, or use it to inform the development of other economic models."*

Since the beginning of the appraisal, and under conditions of secrecy, the Appraisal Committee has adjusted the assumptions used in the economic model to progressively reduce the cost effectiveness of agents. Please see in particular paragraphs 4.3.8 and 4.3.10 of FAD1 and paragraphs 4.3.9 and 4.3.13 of FAD2. Indeed, the patient group initially able to access treatment did not increase as the price of generic alendronate fell[6].

This had the result that since the fully executable model was not available for peer review, it has been impossible for consultees to effectively critique the assumptions and to supply data that might inform deliberations on the assumptions. As a result of the secrecy surrounding the economic model, the resulting economic analysis was overly negative towards treatment with strontium ranelate. Further, the economic model was not able to be fully transparent and it was not possible for stakeholders to consider all the underlying assumptions that were being made. According to section 1.1.1 of the Guide to the Technology Appraisal Process the appraisal process should be carried out in an open and transparent way that allows maximum understanding and input from consultees and stakeholders:

> *"1.1.1 This document sets out the process, including timescales, that the National Institute for Clinical Excellence (NICE or the Institute) follows in undertaking technology appraisals. The purpose of this document is to describe a uniform, open and transparent process by which all technology appraisals are conducted. The process is designed to achieve robust guidance for the NHS, developed in an open and transparent way that allows maximum understanding and input from consultees and stakeholders"*. (emphasis added)

Further, according to section 4.2.3 of the Guide to the Technology Appraisal Process, evidence that is pivotal the to the Appraisal Committee's decisions (i.e. the economic model) should be available:

> *"4.2.3 To ensure that the appraisal process is as transparent as possible, the Institute considers it highly desirable that evidence pivotal to the Committee's decisions should be publicly available. Ideally, all the evidence seen by the Appraisal Committee should be available to all consultees and commentators. Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence')."*

Clearly, as the economic model was published in a limited form, the Institute failed to act in a transparent manner in breach of the published procedure.

The lack of access to the economic model allowed the Appraisal Committee to dominate the decision making on the use and sensitivity analysis undertaken in order to generate extremely critical assumptions in the modelling. For example, the economic analysis failed to consider fall time effectively.

The economic analysis supplied in various forms since the beginning of the appraisal, was unable to consider variation of a critical assumption for the cost effectiveness of agents, including strontium ranelate. The assumption was that the "*duration of*

[6] "GDG response to draft FAD for primary prevention", p12

treatment" equalled the "*duration of fall time"* where "*fall time"* is the quantity of time after treatment had finished that the bone remained protected from fracture by previous treatment. As detailed in the published analysis of strontium ranelate[7], the core assumption of the analysis was five years of treatment resulting in five further years of fall time:

> "*The time horizon of the model was constrained to a 10 year period, owing to the likely treatment effects being confined within this period, as well as uncertainty around future medical costs and technologies that may become available, and the gap in the evidence base concerning the effect of fractures on quality of life after a period of 10 years."*

This assumption is not evidence based and could lead to an erroneous conclusion. Sensitivity analysis to this assumption did not inform the considerations of the Appraisal Committee. The effect of this assumption is that younger patients are much less likely to be cost effective to treat since they are protected only for a period when they have a lower risk of suffering a fracture and when older, their fracture risk returns to that which is normal for their age and other risk factors. It may be the case that five years of treatment results in ten years of fall time. Inclusion of variation of this assumption in the probabilistic sensitivity analysis would have dramatically improved the cost effectiveness of strontium ranelate, along with other drugs.

Without full access to the economic model, it was impossible for the stakeholders to test how important assumptions made by the Appraisal Committee were in the outcome of the economic analysis. Accordingly, the appraisal process was not carried out in an open and transparent manner and maximum input from consultees and stakeholders was not possible.

Our case can be distinguished from the recent Eisai v NICE Case. The Appellant did not have access to the nature of the assumptions that are "at the heart of the Model" (para 61 of the Judgment) and therefore the Appellant had no means of criticising the Model, its approach and the system. The Appellant was clearly denied access to significant information and deprived of the opportunity to make intelligent response.

The High Court judgment in Eisai records that consultees were presented with a read-only model, which, although not fully executable, was at least partly executable. The judgement reported that the consultees were able to view the assumptions underlying the model and that they were only unable to undertake sensitivity analysis. This was not the case with the current appraisal. Consultees were presented with a 'read-only version', which was essentially a series of blacked out inputs and results spreadsheets and did not provide sufficient information to challenge the economic assessment made by the Appraisal Committee. The spreadsheets are not informative about the underlying assumptions and structure of the model. Therefore, they cannot be considered a "model" in any respect, read-only or otherwise.

In summary, the Institute has acted unfairly and not in accordance with published procedures by providing the economic model in a substantially redacted form.

[7] Stevenson, M. S Davis, M Lloyd Jones C Beverley The clinical effectiveness and cost effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. Health Technology Assessment 2007; Vol. 11: No. 4

Therefore, preventing the Applicant from instructing its own experts to check the accuracy of the model used and the overall quality of such a model. Further, the Institute has failed to act in accordance with the principle of transparency.

1.6 The Appraisal Committee has failed to act in accordance with the procedure on innovation

The Institute has failed to act in accordance with the procedure on innovation.

According to Section 6.2.6.9 of the Guide to the Methods of Technology Appraisal, the Institute should be sympathetic to the longer term interest of the NHS in encouraging innovation of benefit to patients.

> *"The Institute also takes into account the longer-term interests of the NHS in encouraging innovation in technologies that will benefit patients".*

Further, this is repeated in the NICE Framework Document[8] and with repeated commitment in public statements[9]. As a new chemical entity, strontium ranelate is manifestly an innovative agent and is the only non-bisphosphonate agent licensed in the prevention of vertebral and hip fractures in post menopausal osteoporosis.

Strontium ranelate is the first in a new class of anti fracture agents for patients with post menopausal osteoporosis and has a totally different mechanism of action, dosing and side effect profile in a market dominated by bisphosphonate therapy.

All evidence provided by the Assessment Groups' economic analysis demonstrated that the *net cost* (incorporating the costs saved from reduced numbers of fractures) and the incremental cost per QALY of strontium ranelate and alendronate compared to placebo have estimates with confidence intervals that fully overlap.

As detailed above, the economic analysis does not incorporate the benefits of making available an innovative agent which is not associated with dyspepsia and so does not necessitate the prescribing of an acid suppressing agent which will negate the reduction in fracture risk resulting from bisphosphonate treatment.

In circumstances where, even under the assumption that acid suppression does not increase fracture risk, clinical and cost effectiveness is, statistically speaking, no different from standard care. Therefore, the Appraisal Committee should advise the NHS that an innovative agent should be made available to patients, who prescribers' judge will benefit from treatment.

A failure to provide access to diversity of treatment is to leave patients exposed to the risk associated with safety issues, such as those detailed above, whilst there are alternative products available which do not have such side effects. Strontium ranelate also provides a benefit when compared with other products as it both stimulates bone

[8] National Institute for Clinical Excellence. Framework Document 2000 http://www.nice.org.uk/pdf/appendixB_framework.pdf

[9] Rawlins M D, A J Culyer National Institute for Clinical Excellence and its value judgments BMJ V. 329 24 JULY 2004

formation and reduces bone resorption, a fact that has been recognised by regulatory authorities such as the EMEA.

In summary, the Institute has failed to act in accordance with published procedure and to recommend an innovative product that would be of significant benefit to patients.

2. Appeal on Ground 2: That the Appraisal Committee has drawn a conclusion that is perverse in the light of the evidence submitted

2.1 The Appraisal Committee has failed to adhere to proper processes for accounting for important scientific evidence

2.1.1 Acid suppression and fracture risk

Substantial evidence on the increase in fracture risk associated with acid suppressant use was submitted on multiple occasions during the appraisal as part of official consultations. Furthermore, evidence demonstrating that fracture risk with concomitant bisphosphonate and acid suppressant use was greater compared with bisphosphonate use alone, was submitted during the preparation of the FAD. Whilst aware of the substantial evidence of the safety risk associated with acid suppression in patients at risk of a fracture, the Appraisal Committee failed to direct the Decision Support Unit ("DSU") to consider the increase in fracture risk associated with the use of acid suppressing agents. Furthermore, the Appraisal Committee at no time directly addressed the points being made, despite the clarity in which they were made and never justified their exclusion from consideration.

2.1.2 Background

The Appraisal Committee commissioned the DSU to undertake a systematic review of the resource use and quality of life effects of gastrointestinal side effects of bisphosphonates[10]. In this review it was noted that prescription event monitoring studies demonstrate the incidence of dyspepsia after initiation of bisphosphonates is approximately five times that seen in comparable patients receiving other prescriptions[11,12]. That side effect is also acknowledged in the SmPCs of the two bisphosphonates considered, alendronate and risedronate[13,14]. It should be noted that by contrast, strontium ranelate is not associated with dyspepsia (see Annex 1 for the SmPC of strontium ranelate)

Further, another independent study has demonstrated that new bisphosphonate users in just the first six weeks of therapy are approximately three times more likely than controls to require acid suppressive medication[15]. Please see in particular paragraphs

[10] Jones M. L. Adverse Effects And Persistence With Therapy In Patients Taking Oral Alendronate, Etidronate Or Risedronate: Systematic Reviews. NHS R&D HTA 2006

[11] Barrera BA, Wilton LV, Harris S, Shakir SAW. 2005. Prescription event monitoring study on 13,164 patients prescribed risedronate in primary care in England. *Osteoporos Int.*, 16, 1989 1998

[12] Biswas PN, Wilton LV, Shakir SAW. 2003. Pharmacovigilance study of alendronate in England. *Osteoporos Int.*, 14, 507 514

[13] Fosamax Summary of Product Characteristics

[14] Actonel Summary of Product Characteristics

[15] Roughead EE, McGeechan K, Sayer GP. 2004. Bisphosphonate use and subsequent prescription of acid suppressants. *Br J Clin Pharm*., 57(6), 813 816.

4.1.5.6 of FAD1 and FAD2. This leads to bisphosphonates being routinely prescribed in conjunction with acid suppressing agents in order to counteract this effect.

A well documented side effect of acid suppressing agents is that they increase the risk of fracture in patients taking them. In support of this, evidence was submitted to the Appraisal Committee in August 2006 clearly demonstrating the relationship between acid suppressing agents (proton pump inhibitors and histamine H_2 antagonists) and increased risk of fracture[16]. Subsequent to this, additional peer-reviewed evidence demonstrating this relationship was submitted to the Appraisal Committee in October 2006[17],[18] and March 2007[19].

[CONFIDENTIAL INFORMATION REMOVED]

Despite investigating the issue of the side effects of bisphosphonates, the Appraisal Committee gave no direction to the DSU to consider the increase in fracture risk associated with the use of acid suppressing agents. Therefore, no account has been taken of this relationship in the clinical or economic analysis conducted by the DSU and the evidence submitted on this point was not considered in the appraisal process. However, this is an essential part of the assessment process as to the determination of the cost effectiveness of a medicine. By not taking into account the cost of acid suppressive medication or the cost of subsequent treatment for the associated side effects, the cost effectiveness of bisphosphonate treatment has been significantly biased. This is in violation of section 1.2.7 of the Guide to the Technology Appraisal Process, which sets out that the evidence should be considered:

> *"The evidence is considered by the Institute's Appraisal Committee (see Box 4.1, page 11), which reaches a judgement as to whether, on balance, the technology can be recommended as a cost effective use of NHS resources in general, or whether it can be recommended for specific indications or subgroups of patients, if this is more appropriate. The Appraisal Committee evaluates the impact on both costs and benefits of any technology under consideration. This judgement is referred to as the appraisal determination, and once the appraisal process is complete, the determination is submitted to the Institute. The Appraisal Committee's determination is the basis of the guidance that the Institute issues to the NHS in England and Wales. See the Institute's Guide to the Methods of Technology Appraisal for further information on the methods used for technology appraisal*".

Further, section 4.5.4.4 of the Guide to the Technology Appraisal Process gives a discretion to the Institute or the Assessment Group to consider relevant reports (e.g. the General Practice Research Database study that was submitted in confidence) while the FAD is being developed.

> *"In exceptional circumstances – for example, if a relevant report is published while the FAD is being developed or as a consequence of comments from consultees or*

[16] Yang Y-X *et al* Chronic Acid Suppression and the risk of Hip Fracture Abstract 861 American Gastroenterology Association March 2005

[17] Yu E.W. C. Shinoff, T. Blackwell, K. Ensrud, T. Hillier, D.C. Bauer. Use of Acid Suppressive Medications and Risk of Bone Loss and Fracture in Postmenopausal Women.

[18] Vestergaard, P., L. Rejnmark, L. Mosekilde. 2006 Proton Pump Inhibitors, Histamine H2 Receptor Antagonists, and Other Antacid Medications and the Risk of Fracture Calcified Tissue International Vol 79:76 83.

[19] Yang Y X, J.D. Lewis, S. Epstein, D.C. Metz. 2006, Long term proton pump inhibitor therapy and risk of hip fracture, JAMA, 296:2947 2953.

> *commentators – the Institute or the Assessment Group may undertake further analysis before the circulation of the FAD. Any such analysis will be distributed to consultees and commentators and posted on the Institute's website at the same time as the FAD".*

[CONFIDENTIAL INFORMATION REMOVED]

In summary, by failing to recognise the exceptional circumstances applied, the Appraisal Committee did not follow their own procedures in considering essential scientific evidence that was submitted. If they had done so, the Appraisal Committee would have reached an entirely different conclusion and the FADs would have been significantly different.

2.2 By ignoring a critical piece of evidence, the Appraisal Committee has made a recommendation that will result in increased expenditure and increased fractures compared to a cost effective alternative.

The Appraisal Committee was made aware on a number of occasions about the risk associated with acid suppression for patients at risk of fracture. Comments were made on multiple occasions during official consultation phases and, later, during the preparation of the FAD that convincing evidence exists that because bisphosphonates increase the risk of acid suppressant use, recommendations should be made that minimise the use of bisphosphonates in patients at risk of or taking an acid-suppressing agent.

The Appraisal Committee chose, without justification, to ignore and, in effect, dismiss this evidence. The result is that physicians are directed by the FADs towards prescribing a medicinal product that will ultimately cause dyspepsia in a percentage of cases with the treatment to counteract this dyspepsia increasing fracture risk. The effect of this increase in fracture risk is that, in some patients, the prescribing of a combination of a bisphosphonate and an acid suppressing agent may increase rather than decrease fracture risk compared to no treatment or alternative medications that do not cause upper gastro-intestinal side effects, such as strontium ranelate

By ignoring this scientific evidence, the Institute has acted against the principle of nonmaleficence and recommended a product that could inflict damage on patients. By failing to act in accordance with the principle of nonmaleficence in ignoring an essential piece of scientific evidence, the FADs prepared by the Institute are perverse.

In January 2005, the NICE Board recommended[20] that Appraisal Committees' account for the principle of "*nonmaleficence"*. In that document, nonmaleficence is described as:

> *"… an obligation not to inflict damage (either physical or psychological) and has often been associated with the maxim "first, do no harm"."*

Furthermore, when this evidence is properly accounted for in an economic model, strontium ranelate can be shown to be cost effective compared to the combination of an acid suppressing agent and a bisphosphonate.

[20] Social Value Judgements – Guidance for the Institute and its Advisory Committees Rawlins 2005

By dismissing a critical piece of evidence, the Appraisal Committee is potentially placing patients at risk:

1. By directing that patients who are at risk of needing acid suppression as a result of taking a bisphosphonate, have no choice but to take a bisphosphonate, the Appraisal Committee are raising fracture risk compared with making strontium ranelate available to these patients; and

2. **[CONFIDENTIAL INFORMATION REMOVED]**

These fractures are associated with significant morbidity and mortality. For example, following a hip fracture there is a 3-fold mortality risk within 6 months[21]. Therefore, one can conclude the FADs in their current format will result in the unnecessary suffering and death of some postmenopausal osteoporotic women, not to mention the increased costs to healthcare resources. Indeed, as the appraisal consultation documents ("ACDS") and FADs have been in the public domain for some time now, this may already have occurred and could continue to occur whilst they remain in the public domain.

In summary, the FADs are negligent in failing to address this issue and are perverse as the Institute failed to act in accordance with the principle of nonmaleficence and the cost effective allocation of scare health service resources by ignoring essential scientific evidence thereby ignoring the needs of a substantial category of patients.

2.3 The Appraisal Committee has demonstrated internally inconsistent decision making with the generalisation of relative risk data generated in low risk patients and extrapolated to all patients under consideration

By failing to accept data from relevant high-risk subgroups, the Appraisal Committee has reached an erroneous conclusion on the measure of effectiveness of the medicinal products reviewed under this appraisal. Therefore, the FADs prepared by the Institute are perverse (in addition to being unfair as discussed in section 1.3 above).

Strontium ranelate has demonstrated a statistically significant reduction in the risk of hip fracture. This effect was demonstrated in a high-risk subgroup in a post hoc analysis requested by the CHMP and the EMEA and published in an eminent peer reviewed journal[22]. These data were the basis for the indication for hip fracture prevention that was recognised by licensing bodies and inserted in the SmPC and have been endorsed by the Scottish Medicines Consortium when it assessed strontium ranelate.

When assessing the efficacy of drugs, the Appraisal Committee established the general principle that it would accept data from high-risk groups, e.g. patients with a previous fracture (along with other additional risk factors), to inform the estimate of

[21] Empana JP. Dargent Molina P, Breart G. J. Am Geriatric Society. 2004; 52(5): 685 90.

[22] This result was published in the TROPOS publication: Journal of Endocrinology & Metabolism, "Strontium Ranelate Reduces the Risk of Nonvertebral Fractures in Post-menopausal Women with Osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) Study", (Volume 90, Number 5, May 2005).

treatment effect for the whole treated population[23]. This assumption was agreed between the Appraisal Committee and the Guideline Development Group. The Appraisal Committee demonstrated this by agreeing to use relative risks of vertebral fracture drawn from high-risk sub populations (patients with a previous fracture) in the modelling of cost effectiveness. The Appraisal Committee agreed to use these data for both strontium ranelate and bisphosphonates[24].

It is clear from the efficacy analysis of the TROPOS trial that the overall population had insufficient power to determine the treatment effect of strontium ranelate in the prevention of hip fracture. However, strontium ranelate demonstrated efficacy in hip fracture in a high risk patient population, one defined not according to fracture status, but according to age and bone mineral density ("BMD") status (over 74 and with a BMD T Score< 2.4)[25]. The Appraisal Committee refused to consider this subgroup analysis as an appropriate measure of efficacy and instead chose to consider a far higher (and non significant) relative risk, which came from a much lower risk population without the power to detect the treatment effect. Please see in particular paragraphs 4.3.23 of FAD1 and 4.3.19 of FAD2.

The Appraisal Committee ignored the fact that the investigators of TROPOS could not effectively pre-specify a high risk subgroup due to the lack of information on which patients constitute a relevant high risk subgroup. This necessitated the need for a post hoc analysis. This fact was recognised by the EMEA in endorsing hip fracture efficacy.

In summary, by the inconsistent consideration of data from high-risk subgroups, the Appraisal Committee has used low risk population data to determine the cost effectiveness of the medicinal products in the appraisal which has led to the FADs prepared being perverse.

3. Appeal Ground 3: The Institute has exceeded its powers

3.1 The Appraisal Committee has amended the scope of the appraisal without direction from the Department of Health and without consultation with stakeholders

The Appraisal Committee has amended the scope of the appraisal by itself without consultation or direction from the appropriate bodies.

As outlined in sections 3.1 3.5 of the Guide to the Technology Appraisal Process, the scope of an appraisal process is produced in consultation with consultees and commentators, the Assessment Group, the Department of Health, the Welsh

[23] Stevenson et al The clinical and cost effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in post menopausal women NHS R&D HTA pub online 19/7/05

[24] For example data from the Fracture Intervention Trial 1 ("FIT 1") study was used to inform the efficacy in vertebral fracture for alendronate when patients were required to have had a vertebral fracture at baseline to enter this study. This also applies to the Spinal Osteoporosis Therapeutic Intervention study ("SOTI") study for strontium ranelate

[25] This result was published in the TROPOS publication: Journal of Endocrinology & Metabolism, "Strontium Ranelate Reduces the Risk of Nonvertebral Fractures in Post-menopausal Women with Osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) Study", (Volume 90, Number 5, May 2005).

Assembly Government and other interested parties. Once the final remit has been produced by the Department of Health and Welsh Assembly Government, the final scope and matrix of consultees and commentators are produced by the Institute. The Ministers then make a final decision on referral to the Institute to begin the appraisal process.

It became apparent after the publication of the latest ACDs that the scope of the appraisal had been amended. As outlined above, this change was made seemingly without a Department of Health direction and without consultation of any third parties.

In summary, this is a clear contravention of standard NICE procedures as outlined above and as such, the Institute has exceeded its powers.

3.2 The Institute has exceeded its powers in taking actions that are not in accordance with the Human Rights Act.

The Institute, as a public body, has not acted in accordance with Articles 8 and 14 of the Convention for the Protection of Human Rights and Fundamental Freedoms (as amended)[26] (as incorporated in the UK by the Human Rights Act 1998).

In particular, the Appraisal Committee deliberately excluded women who do not respond to a treatment with alendronate or cannot tolerate it or for whom alendronate is contraindicated from the right to obtain funded medication from the NHS.

Furthermore, the risk factors included in the FAD for primary prevention are divided into two categories: (i) these associated with the loss of BMD and (ii) these associated with the increased fracture risk. This may result in an arbitrary situation where some women will be entitled to treatment and some others will not.

In addition, the appraisal discriminates on the grounds of age as a woman will only be entitled or not to a funded treatment by reference to her age. This is contrary to Article 14, read together with Article 8, as there is no objective and reasonable justification to this discrimination.

This approach clearly discriminates these categories of patients from the rest of the relevant patient population, which will benefit from funded medicine. Consequently the FADs prevent some patients from having a good quality of life and the ability to live with dignity as laid out in Article 8 and in some cases will result in the unnecessary suffering and death of postmenopausal osteoporotic women.

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[26] Article 8: Right to respect for private and family life which reads as follows:
"*1. Everyone has the right to respect for his private and family life, his home and his correspondence.*
2. There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others."
Article 14 : Prohibition of discrimination which reads as follows:
"The enjoyment of the rights and freedoms set forth in this Convention shall be secured without discrimination on any ground such as sex, race, colour, language, religion, political or other opinion, national or social origin, association with a national minority, property, birth or other status."

All these points constitute a violation of Article 8 and 14 of the ECHR

Conclusion

In conclusion, the Applicant is appealing against the two FADs as published. The Applicant asks the appeal committee to direct that the FADs are reassessed taking into account all evidence submitted, that the Institute uses consistent decision making and appropriate economic models with full transparency in fairness and in accordance with the published procedures and within the remit of the Institute's powers.

5 September 2007

Annex 1

Strontium Ranelate – Summary of Product Characteristics

Annex 2

COMMERCIAL IN CONFIDENCE – NOT FOR DISTRIBUTION

Letter dated 21 May 2007 submitting commercial in confidence data

Annex 3

COMMERCIAL IN CONFIDENCE – NOT FOR DISTRIBUTION

Email dated 7 June 2007 rejecting the new information submitted

Annex 4

COMMERCIAL IN CONFIDENCE – NOT FOR DISTRIBUTION

Email dated 1 March 2007 providing a read only copy of the economic model