Appeal against two final appraisal determinations for the treatment of osteoporosis distributed on 30th June 2008 submitted by Servier Laboratories Ltd

PLEASE NOTE THAT THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION

Appeal

On 30 June 2008, NICE ("the Institute") circulated drafts of 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").

Servier Laboratories Ltd ("the Applicant") welcomes the new analysis and recognises that the guidance contained within the FADs is an improvement for patients in comparison to the previous version of the FADs. However, the Applicant is concerned that the new FADs do not go far enough and, in particular, fail to recommend any publicly funded treatment for osteoporosis in a significant part of the patient population (i.e. those who will not have access to any treatments and those who will only be entitled to receive a single medication which they cannot take).

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

The Appeal Panel's attention is drawn to the Applicant's appeal of the previous versions of the two FADs. Although the Appeal Panel accepted the appeal ground raised by the Applicant and the other appellants that the Appraisal Committee had unlawfully changed the scope of the appraisal (and thus the requirement for the present reappraisal of the FADs), the Panel dismissed the Applicant's other grounds of appeal. Servier disagreed with the dismissal of its other grounds of appeal and has sought to challenge the legality of the Appeal Panel's original decision by way of application to the Court for judicial review on a number of the dismissed grounds of appeal. The proceedings for judicial review remain ongoing.

Some of the arguments raised herein, namely those numbered 1, 2 (in part), 3, 4, 6, 7, 9, 10 and 11 (in part) were raised by the Applicant during the previous appeal. As

stated above, the Applicant disagreed with the Appeal Panel's dismissal of these grounds of appeal. Servier anticipates that the Appeal Panel will regard itself as bound to reject these grounds on the basis of the earlier Panel decision (which, as stated above, is subject to judicial review), but these grounds are included in case the Panel chooses to take a different view.

Executive Summary

The Applicant contends that:

1. The Institute has prepared two FADs that are perverse in the light of the evidence submitted

1. 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 the extrapolation of data from low risk patients to all patients, the Appraisal Committee has reached an erroneous conclusion as to the measure of effectiveness of the medicinal products reviewed in the FADs. This has led the Institute to incorrectly determine that subgroup analysis of high-risk populations was not an appropriate measure of efficacy. In consequence, the Institute has incorrectly concluded that strontium ranelate was not an effective treatment when compared with bisphosphonates.

2. The Appraisal Committee has failed to appropriately account for important scientific evidence

By failing to properly consider important scientific information demonstrating an association between PPI and fracture risk the Institute has failed to make appropriate recommendations for this data in the FADs.

3. The Appraisal Committee has, without justification or clear logical basis, arbitrarily reduced the efficacy of all agents based on an assumption that treatment does not protect patients from risks due to certain risk factors.

Without justification, the Institute has perversely reduced the efficacy for all agents by arbitrarily reducing the treatment effect on fracture risk for all clinical risk factors except age, fracture status and BMD.

4. The Appraisal Committee has demonstrated inconsistent decision making in standards applied both within this appraisal and compared to other appraisals in their application of the hierarchy of evidence

By acting internally and externally inconsistently in their use of the hierarchy of evidence, the Appraisal Committee has ignored better quality evidence in favour of lesser quality evidence. The result of this is that there was a considerable disadvantage for strontium ranelate in the economic analysis. This resulted in the Institute erroneously concluding that strontium ranelate was not cost effective.

5. The Appraisal Committee has been perverse in amending the T-score values

for etidronate, risedronate and raloxifene without justification

The T-score figures for etidronate, risedronate and raloxifene have all been amended without clear explanation so as to artificially improve the cost-effectiveness of all three medicines as against other medicines forming part of the appraisal.

2. 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

6. 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 and therefore the Institute has acted unfairly in this appraisal.

7. The Appraisal Committee has demonstrated inconsistent decision making in standards applied both within this appraisal and compared to other appraisals in the 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. As such, the Institute has failed to act fairly and in accordance with published procedure despite this hierarchy of evidence. 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.

8. The Appraisal Committee has failed to adequately detail the economic analysis undertaken to examine the implications of PPI use in patients taking bisphosphonates

By not providing adequate detail of the additional economic analysis of the implications of fracture risk associated with use of proton pump inhibitors, the Appraisal Committee has failed to act in an open and transparent manner, leading to unfairness and a failure to act in accordance with published procedures when developing the FADs.

9. 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.

10. The Appraisal Committee has failed to act in accordance with the procedure on 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.

3. The Institute has exceeded its powers

11. The Appraisal Committee has exceeded its powers in taking actions that are not in accordance with the Human Rights Act and associated legislation

It is a breach of a patient's right to life for the State (through guidance published by NICE) to refuse to fund medicines for that patient where other patients with the same condition do receive funded treatment, either on the basis of age or an ability to take the recommended first line treatment, in the absence of strong justification. The Institute has therefore exceeded its powers in not acting in accordance with the Human Rights Act and associated anti-discrimination legislation.

Appeal Ground 1: The Institute has prepared two FADs that are perverse in the light of the evidence submitted

Basis for Appeal Ground 1:

1. *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*

1.1 Extrapolation of data from low risk groups

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, and therefore the FADs prepared by the Institute are perverse. In addition, by failing to take into account the degree of clinical need of the patients under consideration, the Institute has not acted in accordance with section 1.2.8 of the Guide to the Technology Appraisal Process. 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[1]. These data were the basis for the indication for hip fracture prevention that was recognised by licensing bodies and inserted in the SmPC.

[1] 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).

Furthermore, these data 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 treatment effect for the whole treated population[2]. 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[3].

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)[4]. 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 paragraph 4.3.27 of both FADs.

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. In addition, the failure to adhere to consistent policy is unfair and not in accordance with published procedure under ground 2 of this appeal.

2. *The Appraisal Committee has failed to appropriately account for important scientific evidence*

As we have highlighted previously, there is evidence of increased risk of fracture associated with PPI use with three independent studies, each with different designs that

[2] 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

[3] 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

[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).

demonstrate statistically significant increases in the risk of fracture in patients taking this class of medication[5,6,7].

In addition to these findings a retrospective cohort study using the GPRD has been conducted to examine fracture risk in patients receiving concomitant bisphosphonate and acid-suppressive medication (ASM)[8]. This research presents evidence that acid-suppressing medication significantly reduces, if not completely negates, the anti-fracture benefits of bisphosphonate treatment.

Servier was pleased to see that the Appraisal Committee had considered these data in the ACDs, and had acknowledged that the various studies showed a trend and concluded that *"caution should be exercised when considering the co-prescription of acid-suppressive medication and bisphosphonates"* (paragraphs 4.3.33 and 4.3.34 of the primary and secondary ACDs, respectively). However, it was Servier's view that the recommendations in the ACDs did not go far enough and, in consultation, stated that it did not understand why the Appraisal Committee had not incorporated the data on increased risk of fracture with concomitant use of PPIs into the overall recommendations of the ACDs. In light of the body of evidence submitted by Servier, which by its nature in identifying an emerging trend is likely to be in the form of cohort and observational studies rather than data obtained from randomised clinical trials, it was perverse for the Appraisal Committed to place such little weight on the data when they demonstrate that a substantial part, if not all, of the efficacy of bisphosphonates is lost when co-prescribed with a PPI.

Furthermore, Servier was concerned that in the absence of any further data to contradict the original appraisal of the data conducted by ScHARR, the Appraisal Committee appears to have backtracked on its initial findings, as set out above. The FADs now state that the *"Committee was not persuaded by this evidence"* and that *"caution should be exercised when considering the evidence about co-prescription of acid-suppressive medication and bisphosphonates*" (emphasis added). In the absence of support for this reverse of position, the Applicant submits the Appraisal Committee irrationally changed this section of the FADs.

Our view is that the current recommendations included in the latest FADs do not go far enough. As we have stated previously, this could be addressed by providing guidance that:

> Patients being considered for anti-fracture treatment and at risk of gastrointestinal side-effects and therefore likely to need to be co-prescribed acid-suppressive medication should be prescribed strontium ranelate.
>
> Patients who are currently taking a bisphosphonate and are co-prescribed an acid-suppressive medication to control the gastro-intestinal side effects of their

[5] 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.

[6] 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.

[7] 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.

[8] De Vries F, Cooper AL, Logan RF, Cockle SM, van Staa TP, Cooper C. Fracture risk in patients receiving concomitant bisphosphonate and acid-suppressive medication or bisphosphonates alone. Osteoporosis Int. 2007; 18(Suppl 3):S261.

bisphosphonate should be switched to strontium ranelate and titrated off the acid-suppressing medication.

3. ***The Appraisal Committee has, without justification or clear logical basis, arbitrarily reduced the efficacy of all agents based on an assumption that treatment does not protect patients from risks due to certain risk factors.***

The assumption of reducing the treatment effect on fracture risk for clinical risk factors other than age, fracture status and BMD status by 50% is totally without evidence base. There is no reason to believe that medications do not lower fracture risk independently associated with risk factors other than age, BMD and fracture status. Furthermore, the selection of a 50% as the assumed efficacy of drugs on fractures associated with these risk factors is, as the Appraisal Committee have admitted (in paragraphs 4.3.13 and 4.3.14 of the primary and secondary FADs respectively), entirely arbitrary.

In the clinical trials of these licensed medicines randomised patients were enrolled with many risk factors apart from low BMD, older age and previous fracture. For example, the clinical trials of strontium ranelate included patients in both arms of the study with *familial history of a hip fracture*, *smoking* and patients with a distribution of body mass indices. *Propensity to fall* was not measured and so, through randomisation, would have been distributed between study treatment arms. A recent examination of the strontium ranelate studies demonstrated that the anti-fracture efficacy of strontium ranelate is independent of baseline risk factors[9].

If medicines are less effective or not effective in reducing fracture risks cited by the Appraisal Committee then they should, consequentially, be more effective than demonstrated in the clinical studies in reducing risk associated with BMD, previous fracture and age. These medicines have demonstrated relative risks in trials where they have been burdened with being tested in populations with fracture risks that the Appraisal Committee alleges they could not, in fact, lower.

Since there is only information on the effect of treatments in populations with all the fracture risk factors identified, it is logical to include all the fracture risk factors that patients are exposed to in the tested and licensed population and to assume that fracture risk reductions are consistent with those demonstrated in the clinical studies. To do otherwise significantly reduces the cost effectiveness of medical treatment unfairly and perversely restricts access to patients who could otherwise benefit from treatment.

Absent any substantiated explanation, it is irrational for the Appraisal Committee to reduce the treatment effect on fracture risk for certain risk factors and to assign these an arbitrary figure instead.

[9] Roux *et al* 2006Vertebral Fracture Risk Reduction With Strontium Ranelate in Women With Postmenopausal Osteoporosis Is Independent of Baseline Risk Factors. Journal Of Bone And Mineral Research. Volume 21, Number 4,

4. ***The Appraisal Committee has demonstrated inconsistent decision making in standards applied both within this appraisal and compared to other appraisals in the application of the hierarchy of evidence***

4.1 Use 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. As such, the FADs prepared by the Institute are perverse.

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-)) in making its appraisal determination and ignored a higher level of evidence (namely, a post hoc study for strontium ranelate (1-) (see paragraph 4.3.27 of both FADs which discussed the TROPOS study)) that had been presented. The Institute also acted internally and externally inconsistently and this is explained further below.

4.1.1 Internal inconsistency

The Appraisal Committee has stated that this 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[10]. However, the Appraisal Committee had previously endorsed the use of the hip fracture data demonstrated by etidronate in an observational study[11].

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.

4.1.2 External inconsistency

Further, there are numerous precedents for the Institute agreeing to use data generated post hoc and, indeed, much lower down the hierarchy of evidence. For example, the Institute agreed to consider the efficacy of imatinib after only open label data had been presented[12].

In the light of this comparison, the decision making calls into question the seriousness with which this Appraisal Committee takes osteoporosis as a disease. Hip fractures, like cancer, can cause death (see paragraph 2.9 of both FADs). It is surprising that the Appraisal Committee did not take this disease seriously enough to extend the same degree of benefit to the sufferers of this condition, as it does to those who are in need of oncology treatments.

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, denying patient access to a valuable alternative treatment where alendronate use is not appropriate. 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*

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

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

[12] "Guidance on the use of imatinib for chronic myeloid leukaemia" Technology Appraisal 70

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 (please see section 6).

5. ***The Appraisal Committee has been perverse in amending the T-score values for etidronate, risedronate and raloxifene without justification***

The Appraisal Committee previously produced ACDs setting out a table of T-scores in various patients which determine whether those patients can be prescribed etidronate or risedronate if unable to take alendronate. These figures were supported by the cost-benefit analysis performed by ScHARR, the results of which were also provided to consultees. Without any evidence base, a large number of these T-scores have been increased in both FADs, enlarging the population of patients able to have access to these two medicines. The figures for strontium ranelate have not been changed. Unless it is the case that these changes are not simply errors to be corrected, it is perverse for the Appraisal Committee to stratify the cost-effectiveness of various treatments in respect of various risk factors and then, without substantiation, arbitrarily amend the results for two of the medicines in this manner.

Furthermore, raloxifene has been recommended as a potential second-line treatment in the secondary FAD even thought there is no evidence for its prevention of hip fracture, indicating that it offers less utility as a treatment for patients with postmenopausal osteoporosis. Strontium ranelate, on the other hand, has a licence for the prevention of both vertebral and hip fracture in such patients. In addition, although cost-effectiveness analysis was produced for raloxifene, indicating that it should not be prescribed except in those patients with extremely low T-scores (even lower than those for which strontium ranelate can be prescribed), the secondary prevention ACD recommends raloxifene simply as an alternative to strontium ranelate in all patients who could be recommended strontium ranelate. It is entirely irrational for NICE to produce a hierarchy of alternative treatments to alendronate based upon the ICER values for those treatments and then allowing one treatment to, in effect, take the benefit of the cost-effectiveness of another.

Appeal Ground 2: 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

Basis for Appeal Ground 2:

6. ***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.***

6.1 Extrapolation of data from low risk groups

As outlined in section 1, 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.

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[13]. These data were the basis for the indication for hip fracture prevention that was recognised by licensing bodies in the SmPC. Furthermore these data have been endorsed by the Scottish Medicines Consortium when it assessed strontium ranelate.

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 1).

7. *The Appraisal Committee has demonstrated inconsistent decision making in standards applied both within this appraisal and compared to other appraisals in the application of the hierarchy of evidence*

As outlined above, 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. As such, the Institute has failed to act fairly and in accordance with published procedure despite this hierarchy of evidence, the Institute took account of a lower level of evidence in making its appraisal determination and ignored a higher level of evidence that had been presented.

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."*

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 <u>supplement</u> the RCT data but not to replace it:

[13] 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).

"3.2.1.3 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."

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. This has had the result of depriving NHS patients from receiving a valuable alternative, in strontium ranelate, when unable to take alendronate. As such, the Institute has failed to act fairly and in accordance with published procedure. The decision is also perverse in the light of the evidence submitted (section 4)

8. *The Appraisal Committee has failed to adequately detail the economic analysis undertaken to examine the implications of PPI use in patients taking bisphosphonates*

8.1 Lack of transparency

The Institute has acted unfairly and in violation of its published procedure by failing to provide adequate detail on the economic analysis of the implications of fracture risk associated with use of proton pump inhibitors.

Section 4.2 (paragraphs 4.2.27 and 4.2.29 of the primary and secondary FADs, respectively) of the FADs references results from an economic analysis that apparently applies the increased risk of fracture resulting from the use of a PPI. No details have been provided on how this economic analysis was done and no opportunity has been given for consultation on the methods used. In these circumstances, it is impossible for stakeholders to comment effectively on the results of this analysis.

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)

By not providing adequate detail of the additional economic analysis, the Appraisal Committee have failed to act in an open and transparent manner, leading to unfairness and a failure to act in accordance with published procedures when developing the FADs.

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

9.1 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 2). 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 4.3.10 and 4.3.12 of FAD1 and paragraphs 4.3.11 and 4.3.15 of FAD2.

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. As set out above, 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 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[14], 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

[14] 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

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.

On a final point, the Applicant draws the Appeal Panel's attention to the Court of Appeal's decision in the case of *R (ota Eisai) v NICE*[15], wherein the Court held that procedural fairness in the context of an appraisal by the Institute requires release of the fully executable version of the economic model used to the stakeholders. Moreover, the decision of the Court of Appeal is not restricted to the facts in that case. Lord Justice Richards specifically referred to the Institute's general policy and the general implications for its work if required to release fully executable versions of the economic models it relies upon to consultees, and thus the wider significance of the Court's decision, when handing down his judgment.

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.

10. *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[16] and with repeated commitment in public statements[17]. 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.

[15] [2008] EWCA Civ 438

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

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

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 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.

Appeal Ground 3: The Institute has exceeded its powers

Basis for Appeal Ground 3:

11. ***The Appraisal Committee has exceeded its powers in taking actions that are not in accordance with the Human Rights Act and associated legislation***

The Institute, as a public body, has not acted in accordance with Articles 2, 3, 8 and 14 of the Convention for the Protection of Human Rights and Fundamental Freedoms (as amended) (as incorporated in the UK by the Human Rights Act 1998). In particular, the Institute has discriminated against patients on the sole basis of their age or disability (breach of Article 14, read in conjunction with either Articles 2, 3 or 8, of the ECHR). Furthermore, the Institute has also failed to comply with its own Equality Scheme (the NICE Equality Scheme and Action Plan 2007-2010), in which it commits to ensuring that it complies fully with duties contained in the equalities and anti-discrimination legislation.

Page 12 of the Equality Plan states:

> "*Our Board is committed to ensuring that we comply fully with the general and specific duties contained in equalities and anti-discrimination legislation and meet the standards with regard to equality expected of all NHS organisations.*
>
> *It is conscious that discrimination can occur inadvertently and has stated that NICE and its advisory bodies should be especially vigilant in avoiding all forms of discrimination.*
>
> *NICE has a primary legal and moral responsibility for ensuring the promotion of race and disability equality and the elimination of discrimination on age and other grounds and that this is met by an effective policy, which is continually monitored*." (emphasis added)

Section 8.1, "Principles informing production and provision of guidance", pp.15 reads as follows:

> "*Age: 'NICE clinical guidance should only recommend the use of a therapeutic or preventive measure for a particular age group when there is clear evidence of differences in the clinical effectiveness of the measure in different age groups that cannot be identified by any other means.*" (emphasis added)

As it stands, the guidance recommends providing access to strontium ranelate to a patient who can not tolerate or is unable to take bisphosphonate medications only if she is at a higher risk of fracture than specified for access to bisphosphonates. Clearly, patient disability is determining access to medical treatment. Patients without this disability (the contraindication to, or intolerance of, alendronate and/or etidronate/risedronate) are able to access medication.

The stratification of patient populations based on age also discriminates against patients on the basis of their age. Two patients who in all material respects differ solely in their age can obtain very different access to the various appraised treatments, and in some cases the difference being that the younger patient would have no access at all to publicly-funded treatment. A limitation of the right of access to funded treatment based on age is not proportionate in circumstances where there are a number of other, equally valid, risk factors such as (1) family history of osteoporotic fractures, (2) pre-existing medical conditions, and (3) smoking, any or all of which could have been used instead of age.

It is a breach of a patient's right to life for the State (through guidance published by NICE) to refuse to fund medicines for that patient where other patients with the same condition do receive funded treatment, either on the basis of age or an ability to take the recommended first line treatment, in the absence of strong justification. The Institute has therefore exceeded its powers in not acting in accordance with the Human Rights Act and associated anti-discrimination legislation.

Conclusion

In conclusion, the Applicant is appealing against the two FADs as drafted. 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.

21 July 2008

Annex 1

Strontium Ranelate – Summary of Product Characteristics

Annex 2

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