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

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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, 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 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.

Executive Summary

The Applicant contends that:

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

   - ***The Appraisal Committee has failed to take account of an important piece of scientific evidence***

   Substantial evidence on the increase in fracture risk associated with acid suppressor use was submitted. **[CONFIDENTIAL INFORMATION REMOVED]** However, 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. The result of this is that the FADs are based on erroneous information and the consequence is that physicians are directed towards prescribing a medicinal product that could ultimately cause dyspepsia and the

treatment to counteract this could increase fracture risk. In addition, 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.

In addition, 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 damage on patients. This has also led the Institute to affect the quality and life of patients and discriminate against patient populations which constitutes a violation of Articles 8 and 14 of the Convention for the Protection of Human Rights and Fundamental Freedoms.

- ***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 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.

- ***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.

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

- ***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 contra indicated 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 only consider drugs for the initiation of therapy for postmenopausal osteoporosis.

In addition, the Appraisal Committee were not consistent with the scope of the FADs as they considered data for alendronate from women who were not osteoporitic and instead had low or normal BMD and osteopenia. This will have significantly biased

the cost effectiveness of alendronate.

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 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. Therefore, the conclusion is that the current FADs do not take into account the needs of an important part of the patient population as they do not recommend any alternative medicinal product to patients yet.

- ***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. 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.

- ***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.

- ***The Appraisal Committee has failed to address new evidence***

By failing to consider new evidence that was submitted on the increase in fracture risk associated with the use of acid suppressing agents, the Institute has acted unfairly by not taking this into account during the appraisal process.

In addition, the Institute has not acted in accordance with published procedure as the evidence impacts on quality of life and the probable effects on mortality was not considered. The consequence of this is that the Institute has conducted a cost effectiveness assessment based on incomplete data which has resulted in a lesser quality of life for some categories of patients by its failure to recommend strontium ranelate. This has also led the Institute to breach Articles 8 and 14 of the Convention for the Protection of Human Rights and Fundamental Freedoms.

- ***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.

- ***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 therapy, in a market dominated by bisphosphonate therapy. The result of this failure to provide access to a diversity of treatment is to leave patients exposed to the risk associated with the bisphosphonate safety profile. As a consequence, the Institute has not recommended an innovative product that is of significant benefit to patients.

3. The Institute has exceeded its powers

- ***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 which has serious side effects, with no other choice of treatment, whilst there is another authorised product, strontium ranelate, which does not have these serious side effects.

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 failed to take account of an important piece of scientific evidence

1.1 Acid suppression and fracture risk

By failing to take account of an essential body of scientific evidence, the DSU has reached an erroneous conclusion on the cost effectiveness of the medicinal products reviewed under this appraisal and therefore, the FADs prepared by the Institute are perverse.

1.1.1 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[1]. 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[2,3]. That side effect is also acknowledged in the Summary of Product Characteristics ("SmPCs") of the two bisphosphonates considered, alendronate and risedronate[4,5]. 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[6]. Please see in particular paragraphs 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[7]. Subsequent to this, additional evidence demonstrating this relationship was submitted to the Appraisal Committee in October 2006[8],[9] and March 2007[10], including peer reviewed articles[9],[10].

[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

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

[2] 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

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

[4] Fosamax Summary of Product Characteristics

[5] Actonel Summary of Product Characteristics

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

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

[8] 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.

[9] 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.

[10] 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.

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 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]

1.1.2 Consequences of failing to consider an important piece of evidence

It results from this that a substantial proportion of the patients who are at risk of needing acid suppression as result of taking bisphosphonates, have no choice but to take an acid suppressing agent. The Appraisal Committee is raising fracture risk in these patients as the efficacy of bisphosphonates will be reduced, if not negated in some instances, due to the increased fracture risk from the acid suppressing agent.

[CONFIDENTIAL INFORMATION REMOVED].

By failing to consider this, the Institute has not properly assessed the degree of clinical need of the patients with osteoporosis as provided in section 1.2.8 of the Guide to the Technology Appraisal Process (this point is further developed in section 7.1):

> "*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*
- *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)

Further, the Institute, as a public body, has not acted in accordance with Article 8 Convention for the Protection of Human Rights and Fundamental Freedoms (as amended)[11] (as incorporated by the Human Rights Act 1998) as the FADs will result in the unnecessary suffering and potential death of a proportion of postmenopausal osteoporotic women. 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.

Further, the discrimination against a sub population of patients who have a pre existing medical condition that are being treated by acid suppressing agents is a violation of Article 14 Convention for the Protection of Human Rights and Fundamental Freedoms[12] as they will be placed at an increased fracture risk compared with patients that are not prescribed acid suppressing agents.

1.2 Violation of the principle of nonmaleficence

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[13] 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"."*

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

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[11] 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."

[12] 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*."

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

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[14]. 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 by failing to consider essential scientific evidence therefore, ignoring the needs of a substantial category of patients. Further, by deliberately failing to take the scientific data into account, the Institute has breached Articles 8 and 14 Convention for the Protection of Human Rights and Fundamental Freedoms.

2. 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

2.1 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 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[15]. These data were the basis for the indication for hip fracture prevention that was recognised by licensing bodies and inserted in the SmPC.

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

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

[15] 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[16]. 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[17].

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)[18]. 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 subgoups, 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 (please see section 5.1).

3. 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

3.1 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.

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[16] 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

[17] 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

[18] 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 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 3.1.1)) in making its appraisal determination and ignored a higher level of evidence (namely, a post hoc study for strontium ranelate (1-) (see section 2.1 which discussed the TROPOS study)) that had been presented. The Institute also acted internally and externally inconsistently and this is explained further below.

3.1.1 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[19]. However, the Appraisal Committee had previously endorsed the use of the hip fracture data demonstrated by etidronate in an observational study[20].

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.

3.1.2 External inconsistency

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

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

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[21].

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 section 1.2 where this point is expanded) and paragraphs 2.9 of FAD1 and FAD2. 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. 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 (please see section 6).

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:

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

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

4.1 The change in the scope of the appraisal

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 contra indicated 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 only consider drugs for the initiation of therapy for postmenopausal osteoporosis.

In addition, the Appraisal Committee were not consistent with the scope of the FADs as they considered data for alendronate from women who were not osteoporitic and

instead had low or normal BMD and osteopenia. This will have significantly biased the cost effectiveness of alendronate.

It only became apparent after 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 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 10.1).

5. 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.

5.1 Extrapolation of data from low risk groups

As outlined in section 2.1, 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[22]. These data were the basis for the indication for hip fracture prevention that was recognised by licensing bodies in the SmPC.

[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).

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 2.1).

6. 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 in section 3, 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:

> *"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. 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 (please see section 3).

7. The Appraisal Committee has failed to address new evidence

7.1 Revision of decisions following new evidence

As outlined in section 1.1.2 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[23]:

> *"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*
> - *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.

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

In summary, the failure to consider the new relevant evidence is unfair, as the Institute has not given proper consideration to the evidence submitted. Further, the Institute has failed to act in accordance with published procedure, as the evidence was relevant to the impact on quality of life and the probable effects on mortality. In addition the FADs prepared are perverse in light of the evidence submitted (please see section 1).

In addition, 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)[24] (as incorporated by the Human Rights Act 1998) as the FADs will result in the unnecessary suffering and death of some postmenopausal osteoporotic women and there will be discrimination against this group of women. Consequently, the FADs prevent patients from having a good quality of life and the ability to live with dignity as laid out in Article 8.

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

8.1 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."*

[24] 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."

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[25].

This had the result that since the fullyexecutable 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 constultees 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.

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

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[26], 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.

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.

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

9.1 Reward of 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.

[26] 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

> *"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[27] and has been repeated this commitment in public statements[28]. 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. Stontium ranelate also provides a benefit when compared with other products as it stimulates bone formation which 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:

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

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

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

10.1 The change in the scope of the appraisal

As outlined in section 4.1, the Appraisal Committee has amended the scope of the appraisal by itself without consultation or direction from the appropriate bodies.

A 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 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.

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.

9 July 2007

PLEASE NOTE THAT THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION

Annex 1

Strontium Ranelate – Summary of Product Characteristics

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Annex 2

COMMERCIAL IN CONFIDENCE – NOT FOR DISTRIBUTION

Letter dated 21 May 2007 submitting commercial in confidence data

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Annex 3

COMMERCIAL IN CONFIDENCE – NOT FOR DISTRIBUTION

Email dated 7 June 2007 rejecting the new information submitted

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Annex 4

COMMERCIAL IN CONFIDENCE – NOT FOR DISTRIBUTION

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