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Dear Elisabeth

Thank you for the opportunity to comment on the health technology appraisal documents recently produced as part of the appraisal of drugs for osteoporosis. Servier have a number of comments that we would like to draw to the attention of the Assessment Group and of the Appraisal Committee.
In summary these comments are:

- The price of generic alendronate has fallen to a level that is 65% of the price of risedronate and will continue to fall significantly over the coming months. This price differential makes it no longer appropriate for the Assessment Group to pool the cost and effectiveness data of these two drugs. Therefore, it is appropriate for the Assessment Group to consider a cost effectiveness of alendronate using the alendronate generic price combined with the alendronate relative risk data. In the light of the size of the risedronate database, sufficient data are available to inform the committee on the cost effectiveness of risedronate in a separate analysis.
- New evidence is enclosed of the increased risk of hip fractures associated with the use of proton pump inhibitors (PPIs) and histamine 2 receptor agonists (H2RAs). In the light of this evidence, Servier requests that patients at risk of fracture and of PPI and H2RA use should not be considered for bisphosphonate therapy and instead be recommended strontium ranelate.
- Evidence is available that demonstrates a significant reduction in the risk of fractures after one year and over 3 and 5 years of treatment in patients 80 years and over. No other osteoporosis treatment has demonstrated vertebral and non-vertebral fracture reduction in women over 80 years old. Servier requests that NICE recognize this efficacy data and recommend strontium ranelate first line in patients 80 years and older.
- Data are available on the reports of breast cancer from the clinical studies in patients taking strontium ranelate. The degree of reduction in reports of breast cancer risk is comparable to the degree of increase in the reports of venous thrombosis embolism (VTE). However, there is no rationale for either side effect

and it is reasonable to assume that both are due to chance. In the light of the equivocal nature of the evidence for VTE risk with strontium ranelate use, Servier requests that the Assessment Group reconsiders allocating the same burden of cost and quality of life reduction to strontium ranelate as is applied to bisphosphonate medication.

Use of Proton Pump Inhibitors in Patients with Post Menopausal Osteoporosis

Two studies have recently been published that highlight issues for the use of PPI or H2RA in patients at risk of an osteoporotic fracture. Yang et al (2005)[1] demonstrated an increased risk of hip fracture associated with the use of both PPI and H2RA medication. O'Connell *et al* (2005)[2] demonstrated a reduction in calcium absorption associated with PPI use, which may partly explain the increased risk of hip fracture Yang et al observed. This is of particular concern for patients who are on bisphosphonates and have a higher concomitant use of PPIs and H2RAs as a result of the bisphosphonate side effect profile.

Yang et al (2005) report an interrogation of the General Practice Research Database for the impact of PPI or H2RA use on the risk of hip fracture. The study concluded that PPI use had an independent relative risk of hip fracture of 2.00 (95%C.I.: 1.77 - 2.25) in patients taking a PPI once a day (or less frequently) and 2.51 (95%C.I.: 1.83-3.45) in patients exposed to a PPI more than once a day. They also defined both dose response and duration of use effects with PPIs. The use of H2RA drugs was also associated with an independent increased relative risk of hip fracture of between 1.32 and 1.64 depending on duration of treatment. The author thus concluded that chronic acid suppressive therapy is associated with an increased risk of hip fracture.

O'Connell *et al* (2005) report the outcome of a trial which assessed the absorption of calcium in patients treated either with a PPI or placebo. The study found that the level of calcium absorption for the placebo arm of the trial was 9.1% while the level for the PPI treated arm was 3.5%. The absolute difference in the rate of absorption was 5.5% (95% CI: 2.1% to 9.0%).

DINLINK data[8] presented to NICE previously demonstrates a clear increase in concomitant prescribing of PPIs associated with the use of bisphosphonates. The systematic review supplied with the HTA report further detailed this.

In view of this evidence it is appropriate that patients requiring treatment for osteoporosis and who have had previous upper gastrointestinal disease, are taking non-steroidal anti-inflammatory agents and/or ant-acid medication, should not be prescribed a bisphosphonate. In these patients, strontium ranelate should be considered the appropriate first line agent.

In addition, patients who have taken a bisphosphonate and, as a result, have suffered upper GI symptoms must not be considered for a second bisphosphonate and/or concomitant PPI or H2RA treatment. These patients should be offered strontium ranelate.

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

[2] O'Connell M,B. *et al* Effects of proton pump inhibitors on calcium carbonate absorption in women: A randomized crossover trial American Journal of Medicine (2005) 118, 778-781

[8] DINLINK Data on File

1 Year Data in Patients Over 80 Years

While women over 80 years represent around 8% of the postmenopausal population, the high prevalence of osteoporosis and incidence of falls in this age group means that they contribute over 30% of all fragility fractures and 60% of hip fractures[3]. This cohort of women is rapidly growing and, consequently, the number of elderly people with osteoporosis is set to markedly rise[4].

A previous submission to NICE from Servier Laboratories Ltd. made available the anti-fracture efficacy in patients 80 years and over after 3 years of treatment. A new analysis[5] is now available that demonstrates efficacy in the prevention of vertebral and non-vertebral fractures after just 1 year of treatment.

The analysis was a pre-planned, intention to treat analysis evaluating the fracture-preventing efficacy of strontium ranelate in patients aged 80 years and over who were enrolled in the SOTI[6] and TROPOS[7] trials. The analysis shows that 1556 of the 6740 (23%) patients enrolled in the SOTI and TROPOS trials were aged 80yrs and over. The baseline characteristics of those receiving strontium ranelate and those on placebo were well matched. The average age was 84 years, with mean T-scores of –3.3 (Slosman reference range which equates to –2.7 on NHAMES III range).

Of these patients, 1448 received more than one sachet of medication, had follow-up X-rays and were analysed for assessment of non-vertebral fractures. 895 patients had vertebral x-rays available and were assessed for vertebral fractures efficacy.

The results of the analysis are set out in the table 1 below.

TABLE 1. RISK OF VERTEBRAL FRACTURE IN PATIENTS 80 YEARS AND OVER. META ANALYSIS OF SOTI AND TROPOS TRIALS

	1 year		3 years	
	Strontium ranelate	Placebo	Strontium ranelate	Placebo
% of patients with vertebral fractures	3.5%	8.3%	19.1%	26.5%
Relative risk of fracture	0.41 [0.22; 0.75] p=0.002		0.68 [0.50; 0.92] p=0.013	
Relative risk reduction	59%		32%	
Absolute risk reduction	4.8%		7.4%	
Number needed to treat	21		14	

[3] Population division of the development of economic and social affairs of the Nations Secretariat, world population prospects: The 2002 revision and world urban prospects (http://esa.un.org/unpp).
[4] Ettinger MP. Aging bone and osteoporosis: strategies for preventing fractures in the elderly. Arch Intern Med 2003; 163:2237-2246
[5] Seeman E et al. Strontium ranelate reduces the risk of fracture in elderly women with osteoporosis in the first year of treatment. Osteoporosis Int 2006; 17 (suppl 1): Abstract OC21 and Journal of Bone and Mineral Research (in press)
[6] Meurnier P J et al. The effects of Strontium Ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl JMed 2004; 350: 459-468
[7] Reginster J Y et al. Strontium ranelate reduces the risk of non vertebral fractures in post-menopausal women with osteoporosis: Treatment Of Peripheral Osteoporosis (TROPOS) study. J Clin Endoc Metab 2005 2005; 90(5): 2816-2822

The results demonstrate an excellent efficacy profile in patients over 80 years, even after just1 year of treatment.

The risk of non-vertebral fracture was also significantly reduced in the strontium ranelate treated patients at one and three years, with a trend towards reduction after only 6 months. The reductions in non-vertebral fractures with strontium ranelate treatment are shown in table 2.

TABLE 2. RISK OF NON-VERTEBRAL FRACTURE IN PATIENTS 80 YEARS AND OVER. META ANALYSIS OF SOTI AND TROPOS TRIALS

	6 months	1 year	3 years
Relative risk of non-vertebral fracture	0.56 [0.30; 1.05] p=0.066	0.59 [0.37; 0.95} p=0.027	0.69 [0.52; 0.92] p=0.011
Relative risk reduction	44%	41%	31%
Absolute risk reduction	1.6%	2.8%	5.5%
Number needed to treat	63	36	18

Analysis of hip fractures demonstrated that after 3 years there was a trend towards reduction in the strontium ranelate treated patients, although this analysis was not powered to investigate this endpoint.

This reduction in incidence of hip fractures with strontium ranelate is shown in the table 3 below.

TABLE 3. RISK OF HIP FRACTURE IN PATIENTS 80 YEARS AND OVER. META ANALYSIS OF SOTI AND TROPOS TRIALS

	3 years	
	Strontium ranelate N=739	Placebo N=749
Number of patients with hip fractures	27	41
Relative risk reduction	0.68 [0.42; 1.10] p=0.112	
Absolute risk reduction	2.2%	
Number needed to treat	48	

Strontium ranelate is the only treatment to have demonstrated anti-fracture efficacy at both vertebral and non-vertebral sites in patients over 80 years of age.

Servier requests that NICE recognize that, as the only osteoporotic treatment with demonstrated anti-fracture efficacy at both vertebral and non-vertebral sites in this important patient group, strontium ranelate should be recommended first line in patients over 80 years of age

VTE and Breast Cancer in Patients treated with Strontium Ranelate

A new meta analysis of safety data available from the trials of strontium ranelate has reported that the reports of malignant breast neoplasms in the strontium ranelate group was 0.4% (14 patients) out of total number of patients in the group of 3352, while the

reports in the placebo-treated group was 0.9% (29 patients) out of the 3317 patients in this group. The confidence interval of the difference is [95%C.I.:-0.92,-0.11].

It is interesting to contrast the breast cancer result with the observed increased risk of venous thrombosis in the same patient population where the relative risk of a VTE was 1.5 [1.1; 2.1]. Furthermore, there is reason to believe that the increased incidence of VTE could be explained by the baseline risk of patients in each treatment group. While a similar proportion of patients in each group were exposed to risk factors for VTE during the study, more patients with previous history of VTE in the strontium ranelate group (3.0%) than in the placebo group (2.4%). This imbalance could have been one reason for explaining that more VTE occurred during studies in the strontium ranelate group, as VTE history is known as one of the major risk factors for VTE recurrence. Indeed, in the subgroup of patients without history of VTE there is no difference between the groups over 3 years with a RR =1.28 [0.87 ; 1.88].

In addition, the rate of VTE in the placebo group was below what is expected in the age population entering the study and the rate for the treatment group falls within this range. Two epidemiological studies' in elderly population reported[8] incidence rates (number of VTE/1000 patients per year): 9.2 to 12.0 in women aged more than 75 and 7.0 in women aged 80 to 84 and 9.7 in women[9] aged more than 85.

The HTA document states that

> …whilst some of the interventions may not be associated with upper GI problems each intervention has a side-effect profile (for example the increased risk of venous thrombosis). It was assumed that the costs and disutilities associated with these conditions were equal to those associated with pooled alendronate and risedronate.

There is no pathophysiological foundation for associating strontium ranelate with either reducing the incidence of breast cancer or increasing the risk of VTE. In light of the equivocal nature of the evidence for an increased risk of VTE and the fact that strontium ranelate has distinct advantages in terms of GI tolerability over alendronate and risedronate, it should not be assumed that strontium ranelate is associated with the same costs and disutilities as alendronate and risedronate are, due to their upper GI side effects.

In summary, Servier request NICE: -

- Recommend that the cost effectiveness of alendronate is considered using the generic price and the alendronate relative risk data.
- Recommend strontium ranelate as the first line treatment in patients who are at risk of fracture and likely to develop GI side effects and require PPI prescription with a bisphosphonate. These patients include those with:

[8] Heit JA., Silverstein MD., Mohr DN., Petterson TM., Lohse CM., O'Fallon WM., Joseph Melton III L. The epidemiology of venous thromboembolism in the community. Thromb Haemost 2001; 86 : 452-463

[9] Oger E. Incidence of venous thromboembolism: a community-based study in western France. Thromb Haemost 2000; 83 : 657-660

    - Previous GI disease
    - Currently taking NSAIDs
    - Currently taking antacids
    - Previous or current use of a PPI or H2RA
- Recommend strontium ranelate as the second line agent of choice after failure of one bisphosphonate due to upper GI side effects.
- Recommend strontium ranelate first line in postmenopausal women over 80 years of age.
- Remove costs and disutilities due to side-effect profile from strontium ranelate.

If you have any questions regarding these data, please do not hesitate to contact me.

Yours truly,