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By email

[REDACTED]

16 February 2012

Dear [REDACTED]

**Re: Assessment Report: Bone Metastases - denosumab**

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 25,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO who produce joint responses to NICE oncological consultations. We are grateful for the opportunity to comment on the above assessment report which has been reviewed by the NCRI Breast cancer Clinical Studies Group (CSG). The comments below are supported by all the organisations listed above.

This is a long, complex and thorough report which includes an assessment of denosumab. Although several members of the NCRI Breast cancer CSG studies group have had significant involvement in a number of studies to do with management of bone problems in breast cancer patients, the distillation of views below has been constructed with the intent of offering an unbiased opinion.

- We note that the only large-scale head-to-head of oral ibandronate and IV zoledronate is the NCRI ZICE trial which is still in follow-up and has not yet reported. Similarly, the limitations due to the lack of direct comparisons between denosumab and bisphosphonates are noted.
- Given the lack of head-to-head data, assumptions on efficacy may not be valid and at the very least our experts believe that a sensitivity analysis should be completed.
- The validity, accuracy and source of the QALY effects of a skeletal complication seemed very arbitrary but are a major driver of the cost effectiveness analyses. For some of the reasons given below this is a major cause for concern.
- The amalgamation of skeletal complications within a 21 day window as a single event, as required by the regulators, leads to a significant underestimate of the real effects of treatment on the number of events and healthcare resource use. Clearly this is not a reflection of the real world, even where multiple events may be linked, from the patient's perspective or from a healthcare resource standpoint, as all such events are individually of relevance. Since the total number of events may not be

apparent from the published trials, the effects and benefits of treatment may be significantly underestimated.

- There is the opportunity for service redesign and the delivery of treatment close to home given that a subcutaneous injection provides potentially a great reduction in patient burden over the long time period compared with 3 to 4 weekly visits for IV therapy. There is some data available suggesting that quality-of-life was better for patients receiving home therapy rather than hospital use (Wardley et al British Journal of Cancer 2005). Unfortunately, this paper is listed as 'no relevant intervention' but is the sole study comparing the quality-of-life for patients with bone metastasis according to where they received the treatment.
- One of the key studies cited comparing pamidronate to placebo (Lipton et al 2000) is not the original trial report but an amalgam of the registration studies by Hortobagyi et al and Theriault et al. As such it misses out on key data including effects on quality of life contained in those original reports.
- Radiotherapy for metastatic disease in current UK practice is a single fraction except for spinal cord metastasis in contrast to statements made in the report.
- The issue of waiting for results as a time factor may not be relevant in UK clinical practice where GP surgeries perform pre- treatment blood tests.
- In calculating costs does treating hypercalcaemia cost the same as an orthopaedic operation?
- The use of arbitrary thresholds of time to first SRE is seemingly based on single clinician's judgement. For patients who live 5 to 10 years with metastatic disease a three-month difference may not be significant. However, it is very different from those who live 5 to 10 months.
- The question of how progression is taken into account (page 128) is a matter for concern since while progression may lead to a change of therapy it is unlikely to change the bisphosphonate use or approach.
- Our experts were puzzled by the quotation of median survival with metastatic disease of 14 months. Certainly for postmenopausal ER positive women the figure is over three years.
- Is there any data to support the statement that 'the risk of an SRE among those discontinuing is assumed to be equal to that for BSC' given that a bisphosphonate will be in the bone for years following administration whereas denosumab may not be?
- With reference to blacked out table 77, our experts consider that most discontinuation of bisphosphonate is either for toxicity or proximity to death and not related to SAE's.
- The assumption that loss of quality-of-life with an SRE starts five months before is considered strange.

While respecting the considerable volume of work presented in this report the above points cause concern to the NCRI/RCP/RCR/ACP/JCCO.

Yours sincerely

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