Novartis Pharmaceuticals UK Ltd
Frimley Business Park
Frimley
Camberley
Surrey GU16 7SR

Dr C M Longson
Director, Centre for Health Technology Evaluation
National Institute for Health and Clinical Excellence
Midcity Place
71 High Holborn
London
WC1V 6NA

9 July 2010

Dear Dr Longson

Re: Single technology appraisal (STA): Denosumab for the prevention of osteoporotic fractures in postmenopausal women - Appraisal consultation document

Thank you for your email dated 11th June 2010 inviting comments on the Appraisal Consultation Document (ACD) and Evaluation Report for the above appraisal. Novartis' comments are as follows:-

1. **UK List Price of Zoledronic acid (Zoledronate) 5 mg (Aclasta®)**

The manufacturer's submission cites the UK list price for zoledronate 5 mg as £283.74 (Table B63, column entitled "mean cost per year", p228). This was correct until the price for zoledronate 5 mg was reduced on 1st January 2010. Since this date, the cost per vial of zoledronate 5 mg has been £266.72.

The manufacturer's submission is dated 15th January, after the price cut was effective, although we acknowledge that publicly available sources of cost information are unlikely to have been updated by this time. The new price does not appear to have been picked up by the manufacturer, the ERG or NICE. The source for drug costs in the manufacturer's submission is the British National Formulary (BNF) September 2009, although we are conscious that the BNF is only updated every 6 months and has a long lead time for updates. This is because it takes the bulk of its pricing data from NHSBS prescription services via the DM+D service (http://dmd.medicines.or.uk) (for example, although communicated to BNF in January 2010, the price change for zoledronate 5 mg will not be reflected in the BNF until publication of BNF 60 in September 2010). Therefore, the BNF is sometimes not the most appropriate source of UK drug cost information for economic evaluations. Cross checking prices with other accepted sources of information for drug costs should have identified the price change prior to the finalisation of the ERG report (dated 23rd March 2010) and the Appraisal Committee meeting (which took place on 27th April 2010). For example, the updated price of £266.72 has appeared in the Monthly Index of Medical Specialities (MIMS) since February 2010.

2. **Wrist Fracture Relative Risk (RR) for Zoledronate**

- "*None of the treatments were associated with a statistically significant decrease in the risk of wrist fracture (RR of 0.84 for denosumab, 0.98 for strontium ranelate and 0.29 for teriparatide; no data were available for zoledronate or raloxifene)"* (ACD point 3.7, p9).....
- "*the relative risk for interventions where data for wrist and hip fractures were not available was assumed to be 1.00*" (ACD point 3.13, p13)

The above statements suggest that the manufacturer's systematic review did not locate any wrist fracture data for zoledronate. Table B21 of the manufacturer's submission (p106-8) indicates that the efficacy data from one study, HORIZON-PFT (Black et al. 2007) provided relative risks (RRs) for zoledronate in the manufacturer's model. This table also confirms that Black et al. (2007) did not report a wrist fracture RR. However, not reporting results at a specific fracture site cannot be interpreted as a complete lack of efficacy at that site. We note that the ERG agreed that this assumption was unreasonable and performed an analysis in which the risk reduction for zoledronate at the wrist was set to 15.8% (i.e. they used the RR of 0.84 reported RR for denosumab).

The list of articles excluded in the manufacturer's systematic review is not provided in the Evaluation Report. However, it is reasonable to expect that a number of articles reporting results from the HORIZON-PFT study (e.g. congress abstracts) were excluded on the basis that they were secondary publications. One of these congress abstracts (Black et al. 2009) reports the effect of zoledronate on a subset of six non-vertebral fractures (wrist, hip, pelvis, humerus, leg and clavicle). Although the abstract only reports fracture reductions at an aggregated level across all six sites, the poster presentation reports the RRs at each fracture site individually. The poster is attached separately and highlights a RR of 0.81 (95% CI 0.62-1.06) (p=ns) for zoledronate at the wrist. This RR is considerably lower than the RR applied by the manufacturer in their model (1.0) and also lower than the denosumab RR (0.84) applied by the ERG to equalise the wrist RRs for the zoledronate vs. denosumab comparison.

We agree with the ERG that it is unreasonable to assume an RR of 1.0 for zoledronate at the wrist based on "lack of evidence" and suggest that the evidence-based RR of 0.81 is used in any future analyses considered by the Appraisal Committee.

3. **Administration Setting (Primary vs. Secondary Care) and Subsequent Administration Cost**

There are a number of references to this issue throughout the ACD, for example:-

- "*Following a request from the ERG, the manufacturer provided an analysis in which the cost of administering denosumab was increased, to assess cost effectiveness if it were delivered in secondary care. Under this scenario, the ICER for denosumab compared with no treatment rose to £36,185 per QALY gained in women with no prior fragility fracture, and to £15,720 per QALY gained in women with a prior fragility fracture. This change led*

to zoledronate dominating denosumab in women with and without a prior fragility fracture." (ACD point 3.23, p17-18)

- "*When the manufacturer increased the cost of administering denosumab (by assuming that it would be delivered in secondary care), this increased the ICER for denosumab compared with no treatment from £29,200 to £36,200 per QALY gained for primary prevention, and from £12,400 to £15,700 per QALY gained for secondary prevention. The Committee noted that given the similar cost and efficacy of denosumab and zoledronate, changes to this assumption also resulted in zoledronate dominating denosumab for both primary and secondary prevention. However, the Committee was mindful that, although licensed for treatment of osteoporotic fragility fractures, the cost effectiveness of zoledronate has not been appraised by NICE*." (ACD Point 4.13, p31-32).

Although we are aware of a handful of centres in which zoledronate is administered in primary care settings, we agree with NICE's assessment that zoledronate is mainly used in secondary care in the UK. From the results provided by the manufacturer, it is clear that, in secondary care settings, zoledronate dominates denosumab for primary and secondary prevention. Thus, in patients for whom treatment in secondary care is most appropriate, zoledronate would be the preferred treatment option. The fact that the "*cost-effectiveness of zoledronate has not been appraised by NICE*" is irrelevant as zoledronate was listed as a comparator in the scope for this appraisal. Zoledronate was reviewed by NICE's Topic Consideration Panel for Long-Term Conditions in March 2007 (NICE 2007); it received a provisional score of 0 (out of 5), with an action specified as follows "*NICE to liaise with osteoporosis GDG as necessary to ensure that this topic is included within the guideline*." This seemed to signal a welcome move to consolidate recommendations on pharmacological treatment options for osteoporosis. However, the Clinical Guideline on Osteoporosis has never materialised and remains "suspended".

Even if NICE cannot make a recommendation for a comparator product within an STA, we suggest that sections 1.1 and 1.2 provides some clarification for end users of the guidance. An additional statement to reflect that a more clinically effective and cost-effective intravenous treatment option is available for patients receiving their osteoporosis treatment in secondary care settings would be helpful.

4. <u>Duration of Treatment Effect for Denosumab vs. Bisphosphonates</u>

We note the following comment in the ACD: "*Treatment was modelled to continue for 5 years by applying relative risks to the estimated baseline risks of fracture in the cohort with osteoporosis. Following the termination of treatment after 5 years, an assumption was made that women would return in a linear fashion to baseline risk levels over 1 year (a return to baseline levels over the course of 5 years was assumed in NICE technology appraisal guidance 160 and 161).*" (ACD Point 3.13, p12).

The manufacturer's submission provides no justification for using a 1 year return to baseline risk for all interventions rather than 5 years. The submission makes numerous references to the observation that the effects of denosumab on bone turnover are fully reversible with

discontinuation and are restored with subsequent re-treatment. Figure B8 in the manufacturer's submission (p98) illustrates this point and supports the assumption of a rapid return to baseline bone mineral density (BMD) at the lumbar spine, total hip and distal radius in patients treated with denosumab. Thus, a one year return to baseline fracture risk may not be an unreasonable assumption for denosumab. However, figure B8 also illustrates that the return towards baseline BMD levels with alendronate is much more gradual than it is for denosumab. The assessment group model that informed TAs 160 and 161 used a 5 year return to baseline fracture risk concordant with the evidence of this more gradual return to baseline for the available treatments at the time (which included the bisphosphonates alendronate, risedronate and etidronate). In this respect, we note the following comments in the European Public Assessment Report (EPAR) for denosumab (European Medicines Agency, 2010):-

- "*Within 12 months of discontinuation of denosumab treatment, BMD returned to approximately baseline levels*" (EPAR, p33)
- "*While bisphosphonates bind to the skeleton and are active for several years after discontinuation, denosumab treatment effects disappear within month [sic] after drug discontinuation*" (EPAR, p34)

Based on this evidence, we suggest that the Appraisal Committee explores the sensitivity of employing a differential timing of return to baseline fracture risk according to treatment type i.e. using a 1 year return to baseline for denosumab and a 5 year return to baseline for bisphosphonates as per TAs 160 and 161.

5. Safety and Tolerability

There are a number of speculative statements about the safety and tolerability of denosumab in the ACD. For example:-

- *"The Committee heard from the clinical specialists that denosumab is a monoclonal antibody that reduces osteoclast activity and hence reduces bone breakdown, that it is the first drug of its class, and that its biological mechanism of action results in targeted therapy with fewer adverse events than other treatments."* (ACD Point 4.5, p27)"

- *"The clinical specialists also stated that although denosumab is a biological agent that also has effects on the immune system, it is specifically targeted for regulating bone cells. The clinical specialists therefore felt that the potential safety concerns associated with other biological agents (such as anti-tumour necrosis factors) may not be applicable to denosumab"* (ACD Point 4.14, p32).

As with any new pharmacological agent with a novel molecular target, the long-term safety implications are uncertain. RANKL is involved in the normal functioning of the immune system and is expressed by activated T cells (Leibbrandt & Penninger, 2008). As acknowledged in the ACD, by targetting RANKL, denosumab also has effects on the immune system in addition to reducing bone resorption. The EPAR for denosumab (European Medicines Agency, 2010) also states that "*RANKL inhibition by denosumab theoretically can be*

linked to an increased incidence of infectious complications and malignancies during denosumab treatment" (EPAR, p41).

We suggest that statements in the ACD regarding adverse effects remain factual and evidence-based. If comparisons are made with the adverse event profile of other treatments, it should be made clear whether the comparisons are with other osteoporosis treatments or biological agents for the treatment of other conditions (this particularly applies to point 4.5 from the ACD cited above).

I hope that these comments are of value. If you require any further clarification, please do not hesitate to contact me.

Yours sincerely

[redacted]

References

- **Black DM, Delmas PD, Eastell R, et al. (2007).** Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*;356(18):1809-22.
- **Black D, Eastell R, Cosman F, Man Z, Bucci-Rechtweg-C, Mesenbrink P. (2009).** Efficacy of once-yearly zoledronic acid 5 mg on a sub-set of six non-vertebral fractures. Available at http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=f6a118a8-e20f-45a3-a03f-d7083bc551ca. Accessed 2 July 2010. Poster #360 presented at: American Society for Bone and Mineral Research 31st Annual Meeting; September 11–15, 2009, Colorado Convention Center, Denver, Colorado, USA.
- **European Medicines Agency (2010).** CHMP Assessment Report for Prolia. Available at http://www.ema.europa.eu/humandocs/PDFs/EPAR/prolia/H-1120-en6.pdf. Accessed 8th July 2010.
- **Leibbrandt A & Penninger JM (2008).** RANK/RANKL: regulators of immune response and bone physiology. *Ann N Y Acad Sci*;1143:123-150.
- **NICE (2007).** Minutes of 16 March 2007 long term conditions topic selection consideration panel meeting. Available at http://www.nice.org.uk/media/CF8/1B/TSMinutes16March2007LTC.pdf. Accessed 2 July 2010.