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Magdalena Ramirez, M.P.A.
Chief Executive Officer



State of New York, Department of Health
Antonia C. Novello, M.D., Commissioner

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August 14, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 00D-1307, CDER 67. Guidance for Industry: "Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis" published on June 14, 2000

I appreciate the opportunity to comment upon the draft guidance for Industry regarding the development of parathyroid hormone. I am Professor of Medicine at Columbia University, College of Physicians and Surgeons NY and Chairman of Medicine at Helen Hayes Hospital. Currently I have an IND for the use of parathyroid hormone in osteoporosis, and have a NIH sponsored clinical trial ongoing. I am also immediate past president of the National Osteoporosis Foundation, and consultant to several pharmaceutical companies with interest in developing pharmaceutical preparations for the treatment of osteoporosis, including the development of PTH and analogues.

Parathyroid hormone offers a different paradigm for the treatment of osteoporosis, since it produces a marked stimulation of bone formation. Unlike current therapeutic options that reduce remodeling, PTH produces an increase in the rate of remodeling and marked increases in bone mass. Two studies have demonstrated reductions in vertebral fractures using PTH, and one of those a reduction in the rate on non-vertebral fractures. With judicious use in clinical practice PTH offers a choice of treatment that can increase bone mass to within the normal range in many patients.

The occurrence of osteosarcoma within rodent models during the toxicological evaluation of PTH is clearly concerning, and one that requires resolution. I have been involved in two separate evaluations of the possibility that this might be relevant to humans. Both these documents, prepared for industry, have been submitted to the Agency. In short we could find no relationship in primary or secondary hyperparathyroidism, or with therapeutic use to date. Mechanistic studies in rodents are ongoing, and it seems prudent to limit the use of PTH to adult humans avoiding the period of growth that seems crucial to the development of these tumors in rodents.

My concerns lie with the further restrictions on PTH use, especially the definition of osteoporosis which would appear to limit PTH use to patients who have both osteoporosis by bone density criteria and fractures. Many patients who receive current therapeutic agents remain at significant risk of fracture, because the agents in use do not provide a stimulus to bone formation and bone density in such patients remains below the normal range (a T-score below -2.5). This population would benefit from PTH. Additionally new patients whose BMD is excessively low and who could not even under the best of circumstances increase their BMD with anti-resorptive agents to close to normal would also benefit from PTH. Finally, there is the group of patients who clearly have fragility fractures, but whose BMD does not qualify them strictly for the diagnosis of osteoporosis, and need to be considered for an agent that can produce marked increment in BMD.

00D-1307

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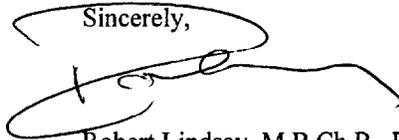
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To allow a patient to suffer an osteoporosis related fracture before consideration for therapy exposes that individual to unnecessary risk. Several studies have demonstrated the effect of a prevalent vertebral fracture on the risk of new vertebral fractures, as well as non-vertebral fractures. Recently, using data from placebo arms of controlled clinical trial, we were able to demonstrate that an incident vertebral fracture further raises the risk, such that 20% of individuals who suffer an incident fracture will fracture again within one year.

I would request that the Agency reconsider the use of the term "severe" osteoporosis., and allow a broader definition of patients who might be allowed into clinical trials, more in keeping with the Phase 3 data for anti-resorptive agents already submitted to the Agency.

I appreciate greatly the chance of commenting on this draft.

Sincerely,

A handwritten signature in black ink, appearing to read "R. Lindsay", written over a circular scribble.

Robert Lindsay, M.B.Ch.B., Ph.D., F.R.C.P.
Chief, Internal Medicine

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