



August 11, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, Maryland 20852

**Re: Docket Number: 00D-1307
Response to FDA's Draft Guidance for Industry entitled
"Development of Parathyroid Hormone for the Prevention and
Treatment of Osteoporosis"**

To Whom It May Concern:

We have reviewed the FDA's draft guidance on the Development of Parathyroid Hormone (PTH) and are providing suggestions for revisions to the document.

Lines 3, 19, and 20

We propose that this guidance applies only to "**fragments and non-natural analogs of hPTH and hPTHrP**" and **NOT** simply to any form of hPTH.

Lines 26, 30, 32, 53, 57, 66, and 70

We propose that the wording in Lines 26, 30, 32, 53, 57, 66, and 70 be changed to specify the agents that caused these osteosarcomas as "**hPTH(1-34) and hPTHrP(1-34)**" and not simply "PTH".

Line 37

We propose that the wording regarding the "impact of these preclinical findings on drug development programs for PTH" be revised to specify "drug development programs for **fragments and non-natural analogs of hPTH and hPTHrP**".

Line 45

We propose that studies to evaluate carcinogenic potential "should generally be done for **fragments and non-natural analogs of hPTH and hPTHrP, but not for hPTH(1-84)**".

00D-1307

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NPS Pharmaceuticals (U.S.)

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Rationale for Changes

The draft guidance does not differentiate between native human PTH, which is an 84-amino acid peptide, and all other fragments and analogs of PTH.

On Line 26, it is stated that osteosarcomas have developed in mice and rats "**...when given PTH and related peptides...**". Although we do not have access to proprietary FDA submissions, it is our understanding that osteosarcomas have been observed only following the administration of hPTH(1-34) and a synthetic analog of the 1-34 region of hPTH-related protein, not the full-length native hPTH or native hPTHrP.

The reason we feel this distinction is important is that a very large number of humans have been exposed to high plasma concentrations of native hPTH(1-84) as a result of primary and secondary hyperparathyroid disease and absolutely no association with osteosarcoma has been observed¹. These patients are not systemically exposed to the fragment hPTH(1-34) since N-terminal fragments formed during hepatic metabolism of hPTH(1-84) are degraded *in situ*.

Other evidence that has been accumulating in the literature very recently, leads us to believe that the osteosarcomas seen in the animal studies may solely be a consequence of the use of these N-terminal PTH (or PTH-like) fragments, **and will not occur with the native hormone**. This opinion is based on the fact that the intact PTH molecule contains a C-terminal region that is known to possess biological activity and, in contrast to N-terminal PTH fragments, is released into the systemic circulation as PTH(1-84) is metabolized. Thus, patients who either receive or generate high concentrations of hPTH(1-84) during pathological conditions subsequently form systemically available C-terminal fragments, whereas patients administered hPTH(1-34) do not.

Although the role of C-terminal PTH fragments in normal physiology remains to be confirmed, evidence is accumulating that they may act to balance the effects produced by the N-terminal region of hPTH(1-84). For example, hPTH(1-34) and hPTH(53-84) produce opposite effects on alkaline phosphatase activity in bone cells². Co-incubation of these cells with equimolar concentrations of both peptides markedly inhibited the response to PTH(1-34)³ alone. Moreover, a novel N-terminally truncated PTH fragment [possibly hPTH(7-84)] has been identified recently. This PTH fragment is a PTH/PTHrP receptor antagonist and has been shown in rats to antagonize the calcemic response to hPTH(1-34)⁴. This suggests that when hPTH(1-84) is released, the subsequent production of systemically available hPTH(7-84), by antagonizing PTH receptors, may act to attenuate the effective duration of the hPTH(1-84) response. It is well recognized that transient exposure to PTH is critical in the anabolic response of bone to the hormone.

Two recent studies have also demonstrated that hPTH(1-84) and its fragments can regulate apoptosis in bone cells. The first study⁵ showed that the administration of hPTH(1-34) to normal or osteopenic mice increased bone mass, an effect they attributed to markedly decreased osteoblast apoptosis and increased osteoblast number. Similar substantial decreases in osteocyte apoptosis were also observed in these *in vivo* experiments. Moreover, these authors also reported that PTH(1-34) inhibited induced apoptosis in several osteoblast and osteocyte cells *in vitro*. Importantly, they showed that PTH(3-34) was ineffective whereas dibutyryl-cyclic AMP mimicked the effect of PTH(1-34). This confirms that the PTH-1 receptor mediates this anti-apoptotic response to PTH(1-34).

The second study⁶ used a different approach to investigate the effects of PTH on apoptosis in bone cells. The authors developed a clonal osteocytic cell line from mice homozygous for ablation of the PTH-1 receptor. Thus, while these cells do not express the PTH-1 receptor, they do express high levels of receptors specific for the C-terminal region of PTH. When these cells were incubated with hPTH(1-84), hPTH(24-84) or hPTH(39-84) a marked increase in apoptosis was observed. This effect was abolished by incubation of the cells with an inhibitor of caspase 3, indicating activation of the caspase cascade by the C-terminal region of PTH. In summary, hPTH(1-34) decreased apoptosis in osteoblasts and osteocytes whereas C-terminal PTH fragments increased apoptosis in osteocytes.

These data provide strong evidence that the N- and C-terminal regions of hPTH(1-84) each play important roles in balancing the effects of the other. Administration of the N-terminal hPTH(1-34) peptide, which cannot subsequently produce corresponding C-terminal fragments, may lead to unregulated osteoblast cell growth, resulting in the observed osteosarcoma. **This is an important observation because osteosarcomas are osteoblastic in origin.** Conversely, administering the naturally occurring full-length peptide hPTH(1-84) feeds into the normal metabolic system, allowing the normal production of fragments and, thus, the normal balance and controls.

Conclusion

In conclusion, administration of hPTH(1-34) and all non-natural analogs of hPTH or PTHrP, has little or no extended human exposure history and, just as with any other xenobiotic drug, the only prediction of human safety for these non-naturally occurring peptides is provided by testing in laboratory animals. In the case of hPTH(1-84), it is not logical to use an animal model to predict what is already known about extended human exposure to intact hPTH(1-84).

References

Copies of the following references are provided.

1. Smith J, Huvos A, Chapman M, Rabbs C, and Spiro R. Hyperparathyroidism associated with sarcoma of bone. *Skeletal Radiol* 1997; 26:107-112.
2. Murray TM, Rao LG, Muzaffar SA, Ly Hao. Human parathyroid hormone carboxyterminal peptide (53-84) stimulates alkaline phosphatase activity in dexamethasone-treated rat osteosarcoma cells *in vitro*. *Endocrinology* 1989; 124:1097-1099.
3. Nakamoto C, *et al.* Individual and combined effects of intact PTH, amino-terminal, and a series of truncated carboxyl-terminal PTH fragments on alkaline phosphatase activity in dexamethasone-treated rat osteoblastic osteosarcoma cells, ROS 17/2.8. *Acta Endocrinol* 1993;128:367-372.
4. Nguyen-Yamamoto L, *et al.* Synthetic carboxylterminal fragments of PTH inhibit the calcemic response to hPTH(1-34) in anesthetized thryoparathyroid-ectomized rats. 82nd Annual Meeting of the Endocrinology Society 2000:p302.
5. Jilka RL, Weinstein RS, Bellido T, Roberson P, Parfitt AM, Manolagas SC. Increased bone formation by prevention of osteoblast apoptosis with parathyroid hormone. *J Clin Invest* 1999;104:439-446.
6. Divieti P, Hamirani S, Bringhurst FR. Intact PTH(1-84) induces apoptosis in PTH1R(-/-) osteocytic cells via the carboxyl-terminal PTH receptor. *American Society for Bone and Mineral Research Abstracts*, 2000.

We appreciate the opportunity to respond to this guidance document and for the Agency's consideration of our response.

Sincerely,



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