
Guidance for Industry

Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis

DRAFT GUIDANCE

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For questions regarding this draft document contact Eric Colman at 301-827-6371.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 2000**

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**U.S. Department of Health and Human Services
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If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

I. INTRODUCTION

This guidance document provides recommendations for sponsors of new drug applications (NDAs) on clinical trials and drug development programs designed to evaluate the safety and effectiveness of parathyroid hormone (PTH) in the prevention and treatment of osteoporosis. This guidance applies to any form of PTH, including all analogs and related drug substances (e.g., PTHrP).

II. BACKGROUND

In preclinical studies previously submitted to the Agency, two strains of rats and one strain of mice developed osteosarcomas when given PTH and related peptides from weaning to 18 months of age. Osteosarcomas occur very rarely in mice and rats and were not observed in the control animals in these studies. Many of the tumors were discovered by direct palpation and were often metastatic at the time of discovery, suggesting that they had been present for a long time. Since rodent life expectancy is about 2 years, the animals in these studies were exposed to PTH for most of their life spans. In some cases, tumors occurred in animals at exposures (AUC) equivalent to those commonly used in clinical studies of PTH in the treatment and/or prevention of osteoporosis.

The clinical relevance of these animal findings is not currently known. This guidance was developed by FDA to clarify the Agency's current thinking regarding the impact of these preclinical findings on drug development programs for PTH for the treatment and/or prevention of osteoporosis.

¹ This guidance has been prepared by the Division of Metabolic and Endocrine Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the use of parathyroid hormone in the prevention and treatment of osteoporosis. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

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III. PRECLINICAL STUDIES

As a result of the concern about carcinogenicity discussed above, studies to evaluate carcinogenic potential should generally be done for PTH and related peptides. These studies may entail unique design features; therefore, considerations to address these concerns should be discussed with the review staff in the Division of Metabolic and Endocrine Drug Products prior to initiation.

IV. CLINICAL STUDIES

Given the uncertain clinical relevance of the findings in rodents, and in an effort to improve the benefit to risk ratio of PTH, it is strongly recommended that participation in clinical studies be limited to adults with severe osteoporosis who have completed bone maturation. For the purposes of this recommendation, *severe osteoporosis* is defined as a lumbar spine or hip T-score of <-2.5 and the presence of at least one clinically manifest, radiographically documented osteoporotic fracture at baseline prior to PTH treatment.

Persons with known Paget’s disease of the bone or with otherwise unexplained elevations of plasma alkaline phosphatase (above the upper limit of normal for the laboratory) should be excluded because of the known association between Paget’s disease and osteosarcoma.

A. Patient Follow Up

Any case of osteosarcoma (or other bone tumor) that develops in a study participant receiving PTH or with previous exposure to PTH should be immediately reported to the drug sponsor and the FDA.

In order to improve the ability to conduct long-term follow-up of patients treated with PTH in clinical trials, sponsors are encouraged to collect unique identifiers (e.g., name, Social Security number) for those study participants who provide their consent, when consistent with local regulations and statutes.

B. Patient Informed Consent Form

Sponsors should include information in the informed consent form about the occurrence of osteosarcomas in rodents and are requested to submit these consent forms to FDA’s Division of Metabolic and Endocrine Drug Products for review.