CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 11/17/95

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 11/17/95

SUMMARY MINUTES

Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes
Endocrinologic and Metabolic Drugs Advisory Committee #61

November 17, 1995
Holiday Inn, Silver Spring
8777 Georgia Avenue, Silver Spring, MD

Members Present
Robert A. Kreisberg, M.D.
Nemat O. Borhani, M.D., M.P.H.
Joanna K. Zawadzki, M.D.
Cathy W. Critchlow, Ph.D.
Robert Marcus, M.D.
Robert Sherwin, M.D.
Jose Francisco Cara, M.D.
Maria I. New, M.D.
Colleen A. Colley, Pharm.D.

FDA Participants
Solomon Sobel, M.D.
Gloria J. Troendle, M.D.
Samarendra Dutta, M.D., Ph.D.
Daniel N. Marticello
Durand M. Hedin, R.Ph.

APPEARS THIS WAY
ON ORIGINAL

Members Absent
Henry G. Bone, III, M.D.
D. Roger Illingworth, M.D., Ph.D.

Executive Secretary
Kathleen R. Reedy, M.S.

These summary minutes for the November 17, 1996 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee were approved on 3/28/96.

I certify that I attended the November 17, 1996 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Kathleen R. Reedy, M.S.
Executive Secretary

Robert A. Kreisberg, M.D.
Acting Chairperson

Endocrinologic and Metabolic Drugs Advisory Committee Meeting #61

November 17, 1995

Open Session

The meeting was held in open session and was attended by approximately 175 persons. Background material was provided to the committee members by the sponsor of NDA 19-975, Slow Fluoride (sodium fluoride USP), the University of Texas Southwestern Medical Center; and medical and statistical reviews and selected scientific articles by the FDA Division of Metabolism and Endocrine Drug Products.

Robert A. Kreisberg, M.D., Acting Chair, called the meeting to order at 8:02 AM and invited Advisory Committee members and participating FDA staff to introduce themselves.

Conflict of Interest

The conflict of interest statement stated that Dr. Robert Marcus was granted a full waiver.

Open Public Hearing

Richard Gelula, Associate Executive Director of the National Osteoporosis Foundation, encouraged primary prevention and early intervention of vertebral fracture; and pointed out the need for an expanded armamentarium of safe and effective treatment for osteoporosis. He noted that all current treatment is anti-resorptive, and the proposed **Slow Fluoride** is the first cell stimulating treatment. He urged approval if the treatment meets established criteria, which the National Osteoporosis Foundation supports.

Mr. Marcus Grodberg, citizen, spent 30 years in industry, dealing with fluoride, beginning with its role in the prevention of dental caries, fluoridated drinking water, fluoride supplement to drinking water. He reviewed the application of the information to bone formation and the research which does not meet FDA criteria, the research with negative results at Mayo Clinic and Henry Ford Hospital, and more recent research at NIH which establishes a dose response curve.

Endocrinologic and Metabolic Drugs Advisory Committee #61

Sponsor Presentation

NDA 19-975, Slow Fluoride (sodium fluoride USP)
University of Texas Southwestern Medical Center

Introduction, Rationale, Clinical Pharmacology and Clinical Efficacy was presented by Charles Y.C. Pak, M.D. Dr. Pak described Slow Fluoride as a formation stimulating agent which promotes osteoblastic bone formation for treatment of post menopausal osteoporosis with prevalent fractures. This is in contrast with other preparations which inhibit bone resorption. The essential feature of the treatment format are delivery of fluoride in a slow release formulation restricting gastrointestinal complication and averting toxic peaks of fluoride in serum. The treatment regimen includes coadministration of calcium citrate and intermittent fluoride withdrawal.

Effects on Bone Structure: Joseph E. Zerwekh, Ph.D. described the four methods of examining histological bone structure used in the trials; electron microscopy, back scattered electron imaging, transmission electron microscopy and bone biopsy. The slides illustrated increase in trabecular thickness and reduction of bone resorption. Images of cancellous demonstrated normal lamellar patterns and indicated a six-fold increase in bone formation rate. Values for cortical thickness exhibited an slight increase.

Effects on Bone Quality: Peter P. Antich, Ph.D. addressed mechanical bone quality, fragility, the relationship to elasticity and breaking strength, measured by ultrasound reflectometry, a non-invasive technique. The trends associated with improved mineralization, a positive correlation with cancellous bone connectivity, trabecular connectivity and decreased resorption were shown in the slow fluoride treatment group.

Clinical Safety Profile: Norman H. Bell, M.D. presented the adverse effect profile of slow fluoride. Minor GI and musculoskeletal complaints were not significant. Hip, non-axial and micro fractures were not significantly different between placebo and drug groups, but these were not from the randomized study. The vertebral fracture rates were also not different.

Comparison with Conventional Fluoride Preparations and Other Treatment Modalities: Frederick R. Singer, M.D., enumerated the available treatments and preventive measures for osteoporosis. Fosamax will increase bone, but the formation stimulators are desirable for severe osteoporosis to increase density. Parathyroid is promising, but Riggs, Meunier and DeDushane are advocates of fluoride therapy, showing some efficacy in prevention. Mamelle study in France, comparing slow with plain and enteric coated fluoride shows a difference in skeletal fluoride correlating with blood levels. Hip fracture comparisons between studies with other treatment modes (Fosamax, calcitonin, estrogen), fluoridated water and slow fluoride showed similar results with incomplete and short term studies.

Summary: Charles Y.C. Pak, M.D., concluded the presentation with the reminder that this proposed treatment stimulated new bone formation and is administered with concurrent calcium intake to accommodate this construction.

FDA Presentation

One or Two Study Issue: Gloria Troendle, M.D., Deputy Director, Division of Metabolism and Endocrine Drug Products presented the legal basis and the policy of the Center for Drug Evaluation and Research for two adequate and well controlled trials as the basis for efficacy. A concern for the potential of chance at the .05 confidence level, the necessity to confirm scientific findings, eliminate bias and ensure accuracy in drug efficacy conclusions was cited. Dr. Troendle listed a number of unusual circumstances where a single trial might be acceptable.

Medical Review: Samarendra Dutta, M.D., Ph.D., Medical Officer, Division of Metabolism and Endocrine Drug Products noted the conflicting data regarding the effect of fluoride on bone mass. He reported studies that show a deleterious effect on bone strength and quality at similar dose levels to the proposed NDA. Dr. Dutta discussed misunderstanding of the term therapeutic window and inadequate sample size of the clinical trials presented by the sponsor, both for statistical power and detailed information.

Biostatistical Review: Daniel N. Marticello, Division of Biometrics, Office of Epidemiology and Biostatistics presented, reviewed and interpreted the statistical data submitted by the sponsor. The results of several statistical analyses applied to the spinal fracture data were detection of a statistically significant difference in favor of slow fluoride over placebo. He discussed relative risk, statistical trends and breakdown of groups by estrogen status. Dan also pointed out the small size of the trial, and the limited data available from the second trial, which will not be completed till 1999.

Discussion

The Committee discussed a number of issues, including the definition of osteoporosis (World Health Organization wording prevailed), and the indication for this application, whether treatment or prevention of osteoporosis (treatment is the indication); asked questions for information and clarification of the sponsor and the FDA review Division staff, then proceeded to answer the questions.

Questions

1. Do results of one controlled clinical trial provide substantial evidence of efficacy of slow fluoride in terms of decrease in the incidence of vertebral fractures in patients with postmenopausal osteoporosis?

YES: 9 **NO: 0**

2. Do results of this trial provide evidence to support selection of slow fluoride 25 mg and calcium citrate 400 mg twice daily as the appropriate dose?

YES: 5 **NO: 4**

3. Do results of controlled and uncontrolled studies demonstrate the long-term safety, particularly with respect to quality of bone and increased incidence of non-axial fractures as reported in previous U. S. trials with sodium fluoride?

YES: 9 **NO: 0**

4. Do the bone biopsy and other biomechanical data adequately demonstrate that bone formed during long-term slow fluoride treatment is normal in quality?

YES: 9 **NO: 0**

Dr. Marcus pointed out that none of the questions asked specifically if the Advisory Committee would recommend approval of the NDA, so after discussion and consensus a fifth question was added.

5. Based on currently available safety and efficacy data and considering the overall benefits and risks of the use of slow fluoride as proposed by the sponsor, do you recommend approval for marketing?

YES: 9 **NO: 0**

The meeting was adjourned at 1:18 pm.