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EFFECT OF CALCIMAR® (CALCITONIN) IN PATIENTS WITH PRIMARY OSTEOPOROSIS

Protocol - Phase III
IND No. 6628-11

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EFFECT OF CALCIMAR^{R} (CALCITONIN) IN PATIENTS WITH PRIMARY OSTEOPOROSIS

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I. INTRODUCTION

Osteoporosis is a disease of unknown etiology associated with loss of bone mass. All components of bone are lost proportionately; hence the percentage composition of osteoporotic bone is approximately the same as that of normal bone. Osteoporosis usually develops gradually as loss of bone mass results from a slight differential in favor of bone resorption over bone formation. Most cases of osteoporosis are primary, not associated with known etiologic factors and are classified as postmenopausal, senile, or idiopathic. Of the factors capable of causing secondary osteoporosis, the most commonly encountered are immobilization and administration of adrenal steroids.

Clinical symptoms of osteoporosis include back pain and skeletal fractures resulting from slight or minimal trauma. Radiographs, particularly of the spine, confirm demineralization and may show evidence of vertebral compression fractures and of hairline or subclinical fractures.

Calcitonin is known to have an inhibitory effect on bone resorption. Its use to retard loss of bone is the basis for evaluating calcitonin in osteoporosis.

Preliminary studies have shown alleviation of pain early in treatment, preceding demonstrable improvement in bone density. These observations need to be verified by controlled trials.

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Calcimar^{R} (synthetic salmon calcitonin, Armour) has been approved for use in treatment of Paget's disease. An extension of its use to other diseases of bone characterized by bone absorption is logical and appropriate.

Evaluation of calcitonin in osteoporosis is considered important because no satisfactory specific therapy presently exists. Preliminary, uncontrolled clinical studies in osteoporosis indicated the drug's safety and potential therapeutic value.

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II. OBJECTIVES

The purpose of this study is to evaluate changes in objective measurements of bone mass resulting from administration of calcitonin in patients with primary osteoporosis.

This protocol proposes evaluation in Phase III of the safety and efficacy of calcitonin in osteoporosis, both for relief of pain associated with osteoporotic changes in the skeleton and for prevention of further loss of bone mass in patients with senescent or postmenopausal osteoporosis.

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III. MATERIALS AND METHODS

A. Selection of Patients

1. Criteria for inclusion

a. Ambulatory out-patients, age 50 to 75, of either sex and any race, seeking medical assistance for alleviation of the symptoms of osteoporosis may be considered for this study.

b. Patients accepted for study will be those experiencing symptoms (bone pain) from primary osteoporosis, ambulatory and judged capable of cooperating for the period of study (two years).

2. Criteria for exclusion

a. Osteoporosis secondary to immobilization, administration of adrenal steroids, or other recognized causes

b. Diseases likely to affect bone metabolism, such as

(1) renal failure

(2) peptic ulcer requiring prolonged antacid therapy

(3) malignancy

(4) hyperparathyroidism

c. Experimental therapy (fluoride, diphosphonates, calcitonin, etc.) for osteoporosis within the past six months

d. Clinically recognized therapy (estrogenic hormones, estrogen-androgen combinations, or anabolic agents) within the past 30 days

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e. History of hypersensitivity to calcitonin

f. Inability to cooperate

g. Any diseases likely to interfere with evaluation of or to prevent completion of the study

3. Concurrent medication

a. Concurrent therapy with agents unlikely to affect bone metabolism will be acceptable. Examples include: *analgesics, antidiabetic agents, cardiovascular drugs, sedatives* or *tranquilizers.*

b. Chronic or continued use of medications likely to affect bone metabolism will exclude the patient from enrollment. Examples of such drugs are: *antacids, antibiotics, diuretics, adrenal steroids,* or *anti-inflammatory agents other than salicylates or acetaminophen.* Similarly, a patient who consistently needs *narcotic analgesics* in amounts sufficient to impair his cooperation with the study will be excluded. Necessary short courses of therapy with any of the aforementioned agents during the study will not invalidate a patient's continued participation, but their prolonged daily administration will necessitate dropping a patient from the study.

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B. Medication and Dosage

1. Test Drug

a. The test drug to be used is Calcitonin Solution (Calcimar^{R}), 200 MRC units per ml, in 2 ml vials, in an isotonic aqueous vehicle containing sodium chloride, sodium acetate and acetic acid, pH 4.2, with 0.5% phenol, U.S.P. as preservative. Vials are to be stored in a refrigerator (2-8°C) and injections, subcutaneously, are to be made without further dilution. Multiple withdrawals from the vial are permissible.

2. Dosage Schedule

a. Patients will be instructed to self-inject 0.5 ml of solution subcutaneously each morning. This volume will provide calcitonin, 100 MRC units.

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IV. STUDY DESIGN, PROCEDURES AND EVALUATION

A. Drug and Control Groups

1. Patients will be randomly assigned to the drug-treated group or the control group.

2. All patients will be given supplementary calcium (lactate, gluconate, or carbonate) 1.0 gm daily in divided doses. In addition, each will receive a multivitamin preparation providing 1,000 units of vitamin D each day. These preparations will be provided by the sponsor.

B. Plan of Study

1. Forty to sixty patients will be studied for a period of two years. Patients will be assigned randomly to either drug-treated or control group.

2. A complete history and physical examination will be performed on each patient before and immediately after the two-year study.

3. Each patient will be re-evaluated by an office visit monthly for the first four months and at intervals of two months thereafter. The following observations will be recorded at each visit:
   a. Height, measured accurately to nearest quarter inch
   b. Weight (nearest pound), blood pressure, pulse rate
   c. Severity of bone pain, graded on scale of 0 to 4 (Appendix A, Sheet 1)
   d. Mobility of patient as related to bone pain, graded on scale of 0 to 5 (Appendix A, Sheet 2)

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e. Any significant changes in condition from previous visits, by history and/or examination

f. Any evidence of side effects or adverse reactions related to the study drug

4. Laboratory studies

a. Laboratory studies performed during a two-week period prior to treatment and after 12 months and 24 months will include:

Complete Blood Count	Total Bilirubin
Sedimentation Rate	SGOT
Urinalysis	LDH
Glucose	Alkaline Phosphatase
Serum Creatinine	Calcium
Uric Acid	Phosphorus

b. Laboratory measurements beyond the normal range for the investigator's institution will be verified by repeating the determinations. If such aberrant levels are verified, the investigator will comment on the significance of the abnormal values. In the case of abnormal levels which represent a change from previously normal values, the investigator will state whether, in his judgment, the change is related to the administration of calcitonin.

5. X-ray films of the thoracic spine and lumbosacral spine, using an aluminum step wedge as the control, will be obtained during a two-week period prior to treatment and repeated at 12-month intervals in all patients.

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The radiologist will compare the films taken before and after therapy without knowledge of the treatment.

6. To assess changes in mineral content of bone, densitometric measurements (Norland-Cameron densitometer) will be performed on the distal shaft of the radius before treatment and at six-month intervals thereafter.

7. Additional (optional) measures of effectiveness:

   a. Estimation of total body calcium by means of total-body neutron activation analysis may be performed at intervals of six months.

   b. Bone biopsies may be obtained before and at the conclusion of treatment in all patients willing to participate in this form of evaluation. Analysis will include microradiography, estimates of trabecular volumes, and/or osteoblast and osteoclast counts.

8. Withdrawal from Study

   a. Appearance of signs or symptoms which, in the opinion of the investigator, could jeopardize the patient's welfare, will be reason to discontinue therapy immediately. In this event, complete physical and laboratory examinations are required and should be fully reported. Appropriate therapy should be instituted and the patient should be carefully

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followed until all signs and symptoms subside. Reactions severe enough to cause discontinuation of therapy should be reported to Armour Pharmaceutical Company as soon as possible.

b. If a patient should withdraw or if the investigator finds it necessary to remove a patient from the study for any other reason after the patient has completed six months or more of the study, every effort should be made to obtain final observations, consisting of physical examination, laboratory determinations, and x-ray studies. (An exception may be made in the case of a patient leaving the study between 12 months and 15 months; in this case the 12-month observations may be used as the final measurements unless the investigator has reason to believe that significant changes have occurred since then.)

C. Evaluation

1. Evaluation of Changes in Mineral Content of Bones

a. The major endpoint of this study will be objective measurement of changes in bone mass or density. The results of periodic x-ray films and bone densitometry, as well as any optional procedures (IV.B.7.), will be tabulated by the investigator on the appropriate forms. (See Appendix A - Case Report Forms.)

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2. Evaluation of Changes in Bone Pain and Mobility

a. Bone pain as a symptom of osteoporosis will be identified by location, type and severity. The presence or absence of recent compression fractures should be recorded because of their importance as a cause of bone pain. Semiquantitative assessment of severity of pain and mobility of the patient should be recorded before therapy and at each subsequent visit.

3. Recording of Laboratory and Clinical Results

a. The sponsor will provide report forms on which all laboratory results and clinical evaluations will be recorded for each patient.

b. As each patient completes the two-year study, the investigator will promptly submit all of the accumulated information for that patient to the sponsor.

c. All reports should be sent by first class mail or air mail to:

William B. Parsons Jr., M.D.
Director of Clinical Research
Armour Pharmaceutical Company
806 Greyhound Tower
Phoenix, Arizona 85077

d. Federal law requires that, following completion of a clinical study, a copy of all records of that study be maintained by the Clinical Investigator

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for a minimum of two years. If requested, the sponsor will, upon receipt of individual case report forms, provide each investigator with a copy of such records for his files.

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SEVERITY OF BONE PAIN FROM OSTEOPOROSIS

	Grade
Severely disabling, *not fully* relieved by more potent analgesics than salicylates and *often* interfering with sleep despite these analgesics	4
Moderately disabling, *usually* relieved by more potent analgesics than salicylates and *sometimes* interfering with sleep despite analgesics	3
Mildly disabling, *usually* relieved by salicylates (or equivalent), not interfering with sleep (with or without analgesics)	2
Not disabling, relieved by salicylates (or equivalent) but requiring this medication for pain at some time	1
No bone pain or analgesic medication	0

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MOBILITY OF PATIENT, AS RELATED TO PAIN

	Grade
Confined to bed by bone pain	5
Confined to bed, chair, or wheel chair	4
Ambulatory but lying down > 12 hrs/day because of pain	3
Ordinary activity limited by pain	2
Able to perform normal activity; certain additional or more strenuous activities limited by pain	1
No limitation of activity by pain	0

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