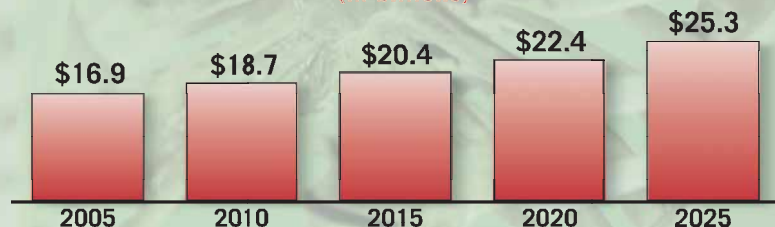


DATA WATCH

Osteoporotic Fracture-Associated Costs Expected to Rise by 49%

(in billions)



Note: Costs were not discounted or adjusted for inflation.

Source: Russel T. Burge, Ph.D., Procter and Gamble Pharmaceuticals

ELSEVIER GLOBAL MEDICAL NEWS

Calcium Limits Fractures in Elderly; Compliance Is Poor

BY ROBERT FINN
San Francisco Bureau

A large, randomized, placebo-controlled trial has confirmed that calcium supplementation in women above the age of 70 can reduce osteoporotic fractures, but the investigators concluded that it would be ineffective as a

public health measure since almost half the women were not compliant.

The study's intent-to-treat analysis demonstrated no overall benefit from calcium supplementation of 1,200 mg per day. But when the analysis was restricted to women who took at least 80% of their tablets, calcium supplementation resulted in a statistically significant 34% decrease in fracture incidence, compared with placebo, Dr. Richard L. Prince of the University of Western Australia, Nedlands, and his colleagues reported (*Arch. Intern. Med.* 2006;166:869-75).

This figure corresponds to an absolute risk reduction of 10.2% in the calcium group vs. 15.4% in the placebo group.

The 5-year study involved 1,460 women with an average age of 75 years who were randomized to receive 600 mg calcium carbonate twice per day or an identical placebo.

Investigators collected data on incident osteoporotic fractures, vertebral deformity, dual x-ray absorptiometry of the hip

and whole body, quantitative ultrasonography of the heel, peripheral quantitative computed tomography of the distal radius, and adverse events.

A total of 236 individuals (16%) sustained 297 incident osteoporotic fractures. After ad-

justment for age, body mass index, and prevalent baseline fractures, the intent-to-treat analysis revealed that calcium supplementation did not significantly reduce fracture risk.

Medication compliance was checked by counting returned tablets in each 12-month review, and average yearly compliance of less than 80% was classified as noncompliant. By this measure, 630 participants (43%) were noncompliant.

When the analysis was restricted to the 830 participants who were compliant, the investigators demonstrated a reduction in all-site clinical fractures (hazard ratio 0.66), appendicular fractures (hazard ratio 0.65), and upper-limb fractures (hazard ratio 0.44).

The investigators recorded 92,000 adverse events, but only constipation was significantly higher in the calcium group (13%), compared with the placebo group (9%).

The investigators concluded that individuals who are compliant, especially if they are under the care of a clinician, can benefit from calcium supplementation. However, they also concluded, "These data should give pause to those who consider that public health policy in this area should be based on epidemiological or surrogate end point data."



BRIEF SUMMARY

Please consult package insert for full Prescribing Information.

INDICATION

EUFLEXXA™ (1% sodium hyaluronate) is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen).

CONTRAINDICATIONS

- Do not use EUFLEXXA™ to treat patients who have a known hypersensitivity to hyaluronan preparations
- Do not use EUFLEXXA™ to treat patients with knee joint infections, infections or skin disease in the area of the injection site

WARNINGS

- Mixing of quaternary ammonium salts such as benzalkonium chloride with hyaluronan solutions results in formation of a precipitate. EUFLEXXA™ should not be administered through a needle previously used with medical solutions containing benzalkonium chloride. Do not use disinfectants for skin preparation that contain quaternary ammonium salts
- Do not inject intravascularly because intravascular injection may cause systemic adverse events

PRECAUTIONS

General

- Patients having repeated exposure to EUFLEXXA™ have the potential for an immune response; however, this has not been assessed in humans
- Safety and effectiveness of injection in conjunction with other intra-articular injectables, or into joints other than the knee has not been studied
- Remove any joint effusion before injecting
- Transient pain or swelling of the injected joint may occur after intra-articular injection with EUFLEXXA™
- Do not use after expiration date
- Protect from light
- Do not re-use—dispose of the syringe after use
- Do not use if the blister package is opened or damaged

Information for Patients

- Transient pain and/or swelling of the injected joint may occur after intra-articular injection of EUFLEXXA™
- As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities or prolonged (i.e., more than 1 hour) weight-bearing activities such as jogging or tennis within 48 hours following intra-articular injection
- The safety and effectiveness of repeated treatment cycles of EUFLEXXA™ have not been established

ADVERSE EVENTS

Adverse event information regarding the use of EUFLEXXA™ as a treatment for pain in OA of the knee was available from two sources; a multicenter clinical trial conducted in Germany and a single center clinical trial that was conducted in Israel.

Multicenter Clinical Investigation

This clinical investigation was a prospective randomized, double blinded, active control (commercially available hyaluronan product) study conducted at 10 centers. Three hundred twenty-one patients were randomized into groups of equal size to receive either EUFLEXXA™ (n=160) or the active control (n=161). A total of 119 patients reported 196 adverse events; this number represents 54 (33.8%) of the EUFLEXXA™ group and 65 (44.4%) of the active control group. There were no deaths reported during the study.

Incidences of each event were similar for both groups, except for knee joint effusion, which was reported by 9 patients in the active control group and one patient in the EUFLEXXA™ treatment group. A total of 160 patients received 478 injections of EUFLEXXA™. There were 27 reported adverse

events considered to be related to EUFLEXXA™ injections: arthralgia – 11 (6.9%); back pain – 1 (0.63%); blood pressure increase – 3 (1.88%); joint effusion – 1 (0.63%); joint swelling – 3 (1.88%); nausea – 1 (0.63%); paresthesia – 2 (1.25%); feeling of sickness of injection – 3 (1.88%); skin irritation – 1 (0.63%); tenderness in study knee – 1 (0.63%). Four adverse events were reported for the EUFLEXXA™ group that the relationship to treatment was considered to be unknown: fatigue – 3 (1.88%); nausea – 1 (0.63%).

Single Center Study

In a single-center, single-blinded, placebo controlled, prospective, two parallel treatment arm clinical trial a total of 49 (25 EUFLEXXA™, 24 placebo) patients were randomized into two treatment groups in a ratio of 1:1 EUFLEXXA™ or placebo. A total of 65 adverse events were reported by 17 (68%) of the patients in the EUFLEXXA™ group and 15 (63%) in the placebo group. Of the 65 total events reported, 20 were regarded as treatment related. Knee pain, hypokinesia of the knee, knee swelling, and rash were considered to be treatment related adverse events.

DETAILED DEVICE DESCRIPTION

Each syringe of EUFLEXXA™ contains:

Sodium hyaluronate	20 mg
Sodium chloride	17 mg
Disodium hydrogen phosphate dodecahydrate	1.12 mg
Sodium dihydrogen phosphate dihydrate	0.1 mg
Water for injection	q.s.

HOW SUPPLIED

EUFLEXXA™ is supplied in 2.25 ml nominal volume, disposable, pre-filled glass syringes containing 2 ml of EUFLEXXA™. Only the contents of the syringe are sterile. EUFLEXXA™ is nonpyrogenic. 3 disposable syringes per carton.

CAUTION

Product contact parts of the syringe contain natural rubber latex, which may cause allergic reactions.

DIRECTIONS FOR USE

- Store at 2°-25°C (36°-77°F). Protect from light. Do not freeze. If refrigerated, remove from refrigeration at least 20-30 minutes before use.
- EUFLEXXA™ is administered by intra-articular injection into the knee synovial capsule using strict aseptic injection procedures. The full content of the syringe is injected into the affected knee at weekly intervals for 3 weeks, for a total of 3 injections.
- If refrigerated, twenty to thirty minutes before use, remove the product box from the refrigerator, remove the blister pack from the box and allow the syringe to come to room temperature. Be sure to return any syringes not intended for use to the refrigerator.

Toll free number for providers and patients to call with questions: 1-(888)-FERRING (1-(888)-337-7464).

MANUFACTURED FOR:

FERRING
PHARMACEUTICALS

FERRING PHARMACEUTICALS INC.
SUFFERN, NY 10901

MANUFACTURED BY:

Bio-Technology General (Israel) Ltd.
Be'er Tuvia Industrial Zone, Kiryat Malachi 83104, Israel

Issue date: 2/06

References: 1. Data on file. Ferring Pharmaceuticals Inc. 2. Kirchner M, Marshall D. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage*. 2006;14:154-162.