

Corporate Report

a report by

Upsher-Smith Laboratories, Inc.

Increasing numbers of physicians are prescribing Fortical® Nasal Spray calcitonin-salmon (rDNA origin) as a safe, effective, and economical brand for the treatment of postmenopausal osteoporosis. Fortical® Nasal Spray, in conjunction with adequate amounts of calcium and vitamin D, is indicated for the treatment of postmenopausal osteoporosis in women greater than five years postmenopause with low bone mass compared with healthy premenopausal women. As the only nasally administered osteoporosis treatment currently available on the market, calcitonin-salmon, the active ingredient in Fortical® Nasal Spray, fulfills a unique role in the management of postmenopausal osteoporosis. The pharmacology, novel manufacturing process, clinical data, favorable safety profile, and convenient administration of calcitonin-salmon is reviewed below.

Pharmacology

The active ingredient in Fortical® Nasal Spray, calcitonin-salmon, is a polypeptide of 32 amino acids in the same linear sequence as calcitonin of salmon origin. The actions of calcitonin-salmon are essentially identical to that of human endogenous calcitonin (a hormone secreted by the thyroid gland that participates in the regulation of bone remodeling and calcium homeostasis). Calcitonin from salmon differs from human calcitonin in that it is more potent and has a longer lasting action, two characteristics that make it more suitable for use as a pharmaceutical agent.

The mechanism by which calcitonin-salmon exerts its anti-resorptive effects in postmenopausal osteoporosis is not completely understood. However, the molecule has been used in clinical practice for more than 20 years. Receptors for calcitonin are located on osteoclasts (cells that resorb bone) and osteoblasts (cells that build bone). *In vitro* studies have shown that calcitonin-salmon inhibits osteoclast function, with a flattening of the ruffled border and a decrease in their overall numbers. There is some evidence from *in vitro* studies that bone formation may be augmented by calcitonin through increased osteoblastic activity. Results from bone biopsy and radial bone mass studies, at baseline and after 26 months of daily

injectable calcitonin, indicate that calcitonin therapy encourages the formation of normal bone.

Manufacturing Process

The US Food and Drug Administration (FDA) first approved calcitonin-salmon nasal spray, manufactured by chemical synthesis, in 1995. Prior to 1995, calcitonin-salmon was available in an injectable dosage form. Advances in biotechnology have led to the development of a rDNA method of manufacturing calcitonin-salmon. Today, calcitonin-salmon manufactured by rDNA technology is utilized in Fortical® Nasal Spray. Fortical® Nasal Spray was approved by the FDA in 2005. The calcitonin-salmon produced by recombinant DNA technology is structurally identical to calcitonin-salmon produced by chemical synthesis.

Disease State Information

Osteoporosis, a medical condition characterized by low bone mass and structural deterioration of bone tissue (diminished bone quality) that predisposes patients to fractures, is a major public health concern. In 2004, it was estimated that 10 million Americans over the age of 50 have osteoporosis. The most common type of osteoporosis is that which occurs in postmenopausal women. Bone loss in postmenopausal osteoporosis is a result of a disproportionate rate of bone resorption (due to increased osteoclast activity) compared with bone formation (decreased osteoblast activity).

Clinical Data

Through its actions on bone cells (diminished osteoclast activity and numbers and possible increased osteoblast activity), calcitonin-salmon nasal spray has been shown to reduce the risk of bone loss by 81% and increase spinal bone mineral density by 1.8–4.2% versus placebo in postmenopausal women with low bone mass over a two-year treatment period.

FDA approval of calcitonin-salmon nasal spray was based on increases in spinal bone mineral density

(BMD) observed in clinical trials. Two randomized, placebo-controlled trials were conducted in 325 postmenopausal women (227 treated with synthetic calcitonin-salmon nasal spray and 98 treated with placebo) over two years. Trial participants were required to have spinal, forearm, or femoral BMD at least one standard deviation below the normal value for healthy premenopausal women. The results of these studies demonstrated that 200 International Units daily of calcitonin-salmon nasal spray increases lumbar vertebral BMD, relative to baseline and to placebo, in osteoporotic women greater than five years postmenopause. Statistically significant increases in lumbar vertebral BMD, versus placebo, were detected as early as six months after initiation of therapy with persistence for up to two years. No effects of calcitonin-salmon nasal spray on cortical bone of the forearm or hip were observed. However, in one study, BMD in a region of the hip with predominantly trabecular bone was significantly increased compared with placebo after one year of treatment. At two years, this trend was no longer significant.

Additional data has been published in the medical literature regarding the impact of synthetic calcitonin-salmon on bone, including its effect on fracture rates, and more recently, its effect on bone quality. Regarding bone quality, a recent study of 91 postmenopausal women with osteoporosis examined the effects of calcitonin-salmon nasal spray versus placebo on the microarchitecture of trabecular bone over a two-year period. Results demonstrated that, regardless of BMD changes, trabecular microarchitecture (e.g. volume, number, spacing, or thickness of trabecular plates) was preserved or improved in the distal radius and/or hip in patients who received calcitonin-salmon, whereas significant deterioration of microarchitecture was noted in the placebo group.

Safety Profile

Fortical® Nasal Spray is contraindicated in patients with clinical allergy to calcitonin-salmon.

Calcitonin is a polypeptide and therefore the possibility of a systemic allergic reaction exists. A few cases of allergic-type reactions have been reported in patients receiving calcitonin-salmon nasal spray, including one case of anaphylactic shock, which appears to have been due to the preservative because the patient could tolerate injectable calcitonin-salmon without incident. With injectable calcitonin-salmon there have been a few reports of serious allergic-type reactions (e.g. bronchospasm, swelling of the tongue or throat,

anaphylactic shock, and in one case death attributed to anaphylaxis). The usual provisions should be made for emergency treatment if such a reaction should occur. For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment.

Formal drug interaction studies with calcitonin-salmon have not been undertaken. To date, no drug interactions with calcitonin-salmon have been observed.

The incidence of adverse effects reported with the use of calcitonin-salmon nasal spray are based on studies involving 341 postmenopausal osteoporotic women exposed to synthetic calcitonin-salmon nasal spray and 131 postmenopausal osteoporotic women exposed to placebo. Most adverse reactions were mild to moderate in severity. Nasal adverse events were the most common reactions reported. Of these events, 70% were mild, 25% were moderate, and 5% were severe in nature with use of calcitonin-salmon nasal spray, and 71% were mild, 27% were moderate, and 2% were severe in nature with placebo. The following adverse events occurred in at least 3% of the patients treated chronically in these studies: rhinitis, symptom of the nose*, back pain, arthralgia, epistaxis, and headache. Calcitonin-salmon nasal spray is not associated with serious drug-related gastrointestinal or esophageal adverse events, venous thromboembolic events, hot flashes, or leg cramps, all of which may be associated with other osteoporosis therapies.

Administration and Dosing

Calcitonin-salmon is absorbed rapidly by the nasal mucosa and quickly enters the bloodstream. Therefore, the intranasal route of administration can be utilized for administration. The recommended dose of Fortical® Nasal Spray is one spray (200 International Units) per day, administered intranasally, alternating nostrils daily. Fortical® Nasal Spray is recommended in conjunction with an adequate calcium (at least 1,000mg elemental calcium per day) and vitamin D (400 International Units per day) intake.

In patients who are prescribed calcitonin-salmon nasal spray, periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum, and mucosal blood vessel status are recommended, and patients should be informed to notify their physician if they develop significant nasal irritation. If severe ulceration of the nasal mucosa takes place, calcitonin-salmon nasal spray should be discontinued. Although smaller ulcers often heal without withdrawal of calcitonin-salmon nasal spray, medication should be discontinued

*Please see Adverse Reactions in the Fortical® Nasal Spray prescribing information for complete list of nasal symptoms.

temporarily until healing occurs. Drug effects may be monitored by periodic measurements of lumbar vertebral bone mass to document stabilization of bone loss or increases in bone density.

Product Facts

Fortical® Nasal Spray is available as a metered dose solution in a 3.7mL fill amber glass bottle. A screw-on pump is provided to attach to the bottle before first use. Following priming, the pump will deliver 200 International Units of calcitonin-salmon per actuation (0.09mL). Each bottle contains enough medication for 30 doses. Fortical® Nasal Spray does not contain benzalkonium chloride. Unopened bottles should be

stored in the refrigerator (between 36 and 46°F). After opening, bottles should be stored in an upright position for up to 30 days at 68–77°F.

Upsher-Smith Laboratories, Inc., marketer of Fortical® Nasal Spray, is a rapidly growing pharmaceutical company that manufactures and markets both prescription and consumer products. Privately held since 1919, the company strives to recognize the unmet healthcare needs of our customers. Upsher-Smith prides itself in providing safe, effective, and economical therapies to the ever-challenged healthcare environment. For additional information about Upsher-Smith and complete Fortical® Nasal Spray prescribing information, visit <http://www.upsher-smith.com/products/fortical.html>. ■

References

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