SUMMARY OF PRODUCT CHARACTERISTICS

OSTEOFORTIL

Teriparatide (recombinant DNA origin) 250 µg/mL

Solution for injection

Therapeutic classification: ATC Code: H05AA02

Description

Osteofortil® is a solution for injection supplied in two presentations: vial or prefilled siringes (See in detail in section "How supplied").
Each vial contains 750 µg of teriparatide. Each prefilled syringe contains 20 µg pf teriparatide. In both presentations, the teriparatide concentration is the same: 250 µg/mL.

Therapeutic action

Teriparatide is a human parathyroid hormone (PTH) analogue.
This 84-amino acid hormone is produced by parathyroid glands and plays a very important role in the bone formation process in kids during growth and to preserve bone resistance in adults and maintain normal calcium levels in circulating blood.
Teriparatide produced by recombinant DNA technology in E. coli is identical to the 34-amino acid N-terminal sequence of endogenous human parathyroid hormone. Teriparatide exerts all the actions of parathyroid hormone and consequently it is used to maintain normal levels of calcium in patients who do not have parathyroid gland, to increase bone strength and reduce the risk of fractures in individuals at high risk.
Consequently, this product is mainly used to treat osteoporosis.
Osteoporosis is a condition of weak bones, which results in bone fragility resulting in fractures. This condition, rare in men, is more frequent in postmenopausal women. Oseoporosis is also a frequent condition of patients on corticosteroid therapy

Indications

- Postmenopausal women with history of osteoporotic fracture.
- Patients on sustained corticoid therapy (5 mg of prednisone or its equivalent for more than 3 months).
- Postmenopausal women and men with severe osteoporosis (defined as more than one fracture due to bone fragility and very low bone density (Tscore < -3.5).
- Women over 65 years old with Tscore <2.5 and previous vertebral fracture.

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Pharmacological action

Teriparatide binds to the same receptors as PTH (called PTHR1 and PTHR2 for parathormone receptor 1 and 2, respectively), with similar affinity and efficacy as PTH. As consequence of activation of these receptors, teriparatide exerts the same effects as endogenous PTH.

Among its effects, actions on phosphor-calcium metabolism and bone function, which are mainly mediated by PTHR1, are the most outstanding effects. PTH maintains calcium homeostasis stimulating calcium and phosphate release from the bone, promoting calcium reabsorption by the kidneys and inhibiting renal phosphate reabsorption. PTH also increases synthesis of 1.25-dihydroxi-vitamin D which in turn increases intestinal absorption of calcium and phosphate. The net result of PTH actions are increase of serum concentration of calcium and the reduction of phosphate. Prolonged elevation of PTH concentration (for instance, primary hyperparathyroidism) causes bone resorption, reduction of bone mineral density, hypercalcemia, hypercalciuria and nephrolithiasis. On the contrary, administration of a single daily injection of teriparatide results in a transient plasma concentration (with a very short mean life) and in that condition only the bone anabolism effect and increase of bone mineral density are observed.

Pharmacookinetics

Teriparatide is administered by parenteral route and rapidly passes to circulating blood from where it is eliminated by hepatic and extrahepatic clearance (approximately 62 l/hour in females and 94 l/hour in males). Distribution volume is approximately 1.7 l/kg. teriparatide half-life is approximately 1 hour when administered by subcutaneous route. No metabolism or excretion studies with teriparatide have been conducted though it is believed that the peripheral metabolism of parathyroid hormone takes place mostly at kidney and liver.

Dosage and mode of administration

Posology

The recommended dose of Osteofortil® is 20 micrograms, administered once daily by subcutaneous injection into the thigh or abdominal wall.

Total treatment duration should not exceed 24 months. Patients should not receive more than a 24-month cycle of teriparatide

treatment in a lifespan.

In case the patient fails to receive Osteofortil® injection at the habitual time, injection should be administered as soon as possible within the same day. Double doses of Osteofortil® should not be injected to make up for non-injected doses.

Osteofortil® should not be injected twice daily.

Mode of use and instructions

When the dose to be administered is from the vial presentation, the cap should be thoroughly cleansed with an isopropyl alcohol embedded swab or gauze pad, after which with the aid of a syringe recommended by the treating physician withdraw 80 µl of the solution for injection, which is the volume that contains 20 µg (recommended daily dose). For vial presentation, the product should be kept in refrigerator immediately after use.

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A new needle should be used for each injection.
In case the prefilled syringe presentation is used, each prefilled syringe should be administered daily.
In order to assess a correct dosing and before administering the injection, it is recommended to remove the needle guard and holding the syringe vertically with the needle pointing up slowly pull the plunger down less that a centimeter length and gently tap the syringe in order to remove bubbles. Then, slowly push the plunger up to force the air bubbles out until the first drop of solution appears. Finally, proceed to inject Osteofortil®.

Contraindications

- Hypersensitivity to teriparatide or to any of its excipients
- Pregnancy and nursing
- Preexisting hypercalcemia
- Severe renal failure
- Patients with metabolic bone conditions other than primary osteoporosis or corticoid-induced osteoporosis, including hyperparathyroidism and Paget´s disease of bone.
- Unexplained elevations of alkaline phosphatase
- Patients with prior external radiation or localized radiotherapy involving the skeleton.
- Patients with bone tumors or bone metastases should be excluded from teriparatide treatment.

Warnings and precautions

Patients should be warned against using this product if previously diagnoses bone cancer or other types of cancer involving the bones. Osteofortil® should not be given to patients with Paget's disease of bone or unexplained elevation of alkaline phosphatase. Neither to patients with other bone diseases.
Patients with bone diseases other than osteoporosis should be excluded from treatment with Osteofortil®. Consequently, in case of doubt contact your physician. Patients who have received radiation therapy involving skeleton are prevented from using Osteofortil®.
In case a patient is dizzy after administration of Osteofortil® injection, they should sit or lay down until the symptoms resolve. In case no relief is observed, patients should be instructed to consult a physician before continuing treatment.
In order to help a patient remind Osteofortil® injection, patients should be instructed to administer injection every day at the same time. This medicine can also be used during food intake or far from meal time.
Patients should be reminded that the medicine has been prescribed only to treat their current medical condition and it should not be recommended to other people.

Carcinogenesis, mutagenesis and impairment of fertility

Teriparatide was not genotoxic in any of the standard battery of tests. Rats treated throughout their life span with daily injections showed exaggerated, dose-dependent bone formation, and an increased incidence of osteosarcoma probably due to an epigenetic mechanism. Teriparatide did not increase the incidence of any other kind of neoplastic condition in rats. Due to the differences in bone physiology between rats and humans, the clinical relevance of these findings is probably scarce. No

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bone tumors were observed in female oophorectomized monkeys treated for 18 months with teriparatide. Besides, no osteosarcoma occurrences have been observed during the clinical trials or during post treatment follow up study. However, primary or secondary bone cancer as well as prior bone irradiation would contraindicate the use of Osteofortil®.

Pregnancy

Teriparatide did not cause teratogenesis in rats, mice or rabbits.
No significant effect in pregnant rats receiving teriparatide at daily doses of 30 to 1,000 micrograms/kilogram. However, pregnant rabbits which received teriparatide at daily doses of 10 to 100 µg/Kg experienced foetal resorption and reduced litter size. Embriotoxicity observed in rabbits can be related to its higher sensitivity of PTH effects on the calcium ion in blood compared to that of rodents.
Essentially the effect of teriparatide on fertility, pregnancy or nursing is unknown in humans. Even though most users are foreseeable menopausal women, some may be in fertile age (for instance women on corticoid therapy. Patients are recommended not to use Osteofortil® if they are pregnant or nursing.
They are also encouraged to comment the treating physician if they are nursing or if they plan to. Women in fertile age should use efficient contraceptive methods during Osteofortil® treatment. Should pregnancy occur, Osteofortil® treatment should be discontinued.
It is not known whether Osteofortil® is excreted in human milk.

Pediatric population

The safety and efficacy have not been established in any pediatric population. Osteofortil® should not be prescribed in children (under 18 years old) or young adult patients with open epiphyses.

Geriatric population

It is foreseeable that most patients on Osteofortil® be postmenopausal elderly women.
In a clinical trial the influence of age on teriparatide effect was evaluated by analyzing response in women under or above 75 years old. No significant interactions between age and treatment was found in bone turnover markers, bone mineral density at thigh bone neck, vertebral fractures, non-vertebral fractures due to bone fragility, weight loss, hyperuricemia or hypercalcemia. However, there was interaction of bone mineral density at lumbar vertebrae (explained by authors as the result of a larger placebo group). When assessing safety, no interaction was observed between treatment and age. Authors concluded that age does not affect efficacy or safety of teriparatide in postmenopausal women with osteoporosis. An European study conducted on octogenarian population with osteoporosis did not identify any special risk on this age group.

Use in liver and renal impairment

Caution is recommended when administering the medicine in patients with mild renal impairment and it should be avoided in severe impairment.

ADVERSE REACTIONS

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As any other medicine, Osteofortil® may have side effects in some patients. The most relevant include gastrointestinal disorders including nausea, reflux and hemorrhoids, fast heartbeat, dyspnea, headache, fatigue, asthenia, depression, dizziness, vertigo, anemia, increase in sweating, muscle cramps, myalgia, arthralgia, sciatic pain.

Most frequent side effects (more than 10% of treated individuals) are general malaise, headache, dizziness and upper and lower limbs pain.
One to 10% of patients undergo an increase of blood cholesterol levels, depression, neuralgic pain in lower limbs, fainting, palpitations, sweating, clamps, energy loss, asthenia and chest pain.
Less frequent side effects (less than 1% of treated individuals) include myalgia, arthralgia, oedema mainly in hands and feet.
Increase of cardiac frequency, low arterial tension, acidity, hemorrhoids, urinary incontinence, polyuria, weight increase, reaction at the site of injection.
For the latter, some persons may experience reddening, skin, swelling, itching, hematomes or slight bleeding around the injection site. They generally disappear within days or weeks; should they persist, consult the physician.
In some patients on teriparatide treatment an increment in blood calcium levels has been observed.
Teriparatide may cause an increase of alkaline phosphatase levels.
Some patients (1 to 10 per 10,000 treated individuals) have experienced allergic reactions immediately after teriparatide injection, which include difficulty in breathing, face swelling, skin rash and chest pain.

STORAGE CONDITIONS

Osteofortil® should be always kept in refrigerator (between 2º C and 8º C).
For vial presentation, Osteofortil® can be used during 28 hours after the first injection, as long as vials have been kept stored between 2°C and 8 °C (in refrigerator).
Osteofortil® should not be frozen. Product vials or prefilled syringes should not be located near the freezer to prevent freezing. Osteofortil® should not be used if it is or has been frozen.
After the 28-day use period, vials should be properly discarded even if still containing some unused solution.

Manufactured by:
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