ELISIUM

MARVIL® 70
ALENDRONATE 70 mg

Prescription only medicine
Made in Argentina

Coated tablets

COMPOSITION
Each coated tablet contains:
Alendronate (as alendronate monosodium trihydrate 91,37 mg).....70,00 mg
Excipients: Cellactose 193,63 mg, Croscarmellose sodium 9,00 mg, Colloidal silicon dioxide 1,50 mg Magnesium stearate 4,50 mg, and Opadry YS-1 White 10,00 mg, Opaglos .....q.s.

THERAPEUTIC ACTION
Non-hormonal specific inhibitor of bone resorption. **Antiosteopenic and antiosteoporotic**.

ATC CODE
M05B A04.

INDICATIONS
MARVIL 70 is indicated for the *treatment of osteoporosis* in postmenopausal women with low bone mineral density of at least 2 standard deviations below the mean value for premenopausal women, or with history of osteoporotic fracture.

PHARMACOLOGICAL ACTION
MARVIL 70 (alendronate monosodium) is an aminobisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that show strong affinity for the hydroxyapatite in the bone.
At the tissue level, alendronate distributes preferentially to sites of bone resorption, where it inhibits the osteoclast activity at the ruffled border level. Alendronate inhibits the osteoclast activity but does not interfere with osteoclast recruiting or adherence to bone surface. Once incorporated into the bone matrix, bisphosphonates are pharmacologically inactive and, hence, should be continuously administered to inhibit osteoclast activity in newly formed areas of bone resorption.
Histomorphometric studies in animals indicate that alendronate treatment reduces the number of sites showing bone remodeling and, subsequently, reduces bone turnover. Moreover, bone formation exceeds bone resorption at these sites, leading to a progressive increase of bone mass.
Alendronate increases bone mass of vertebra and hip, and reduces the incidence of osteoporotic fractures.
Double-blind, placebo-controlled clinical studies have shown the efficacy of alendronate 10 mg/day during 2-3 years for the treatment of osteoporosis in postmenopausal women. These patients evidenced a significant increase of bone mineral density at lumbar spine, femoral neck and trochanter compared with placebo-treated patients. Moreover, studies on fracture incidence in postmenopausal women with or without spinal fractures have shown that long term treatment with alendronate 5 or 10 mg/day during 3 years significantly reduces the rate of patients with new spinal fractures, and the total number of fractures in relation to the placebo-treated group.
The administration of alendronate 70 mg/week has shown to be therapeutically equivalent to the continuous administration of alendronate 10 mg/day.

PHARMACOKINETICS
Mean bioavailability of alendronate 5 and 70 mg administered after an overnight fast and two hours before breakfast was of 0,64% and was similar for men and women.
Concomitant administration with coffee or orange juice reduces alendronate bioavailability by approximately 60%.
Studies in animals indicate that alendronate preferably distributes to the bone and only a small portion distributes to soft tissues. No metabolites have been detected. Though 80% of orally administered alendronate circulates bound to plasmatic proteins, alendronate occupies only a small fraction of such proteins due to its poor bioavailability, determining a minimum potential of interference with other drugs.
After a single IV dose of labeled alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in feces. Moreover, plasmatic concentrations dropped by more than 95% within 6 hours following a single IV dose of alendronate 10mg. Estimated terminal half-life in humans exceeds 10 years, probably due to release of alendronate from the skeleton.
Children: alendronate pharmacokinetics has not been studied in patients under 18 years of age.
Geriatric: bioavailability and urinary excretion in elderly patients was similar to that of younger patients.
Renal insufficiency: No clinical data is available but, probably, alendronate elimination may be reduced in patients with renal insufficiency thus leading to alendronate accumulation in bone.
MARVIL 70 should not be administered to patients with severe renal insufficiency (creatinine clearance <35 mg/ml) due to lack of experience in these cases.
Hepatic insufficiency: Alendronate is not metabolized o excreted in the bile, therefore no pharmacokinetic studies have been performed in patients with hepatic insufficiency.

DOSAGE AND ADMINISTRATION
Recommended oral dosage is one 70mg tablet once weekly.
MARVIL 70 should be taken in the morning after an overnight fast, with a full glass of demineralized water, at least half an hour before breakfast or other beverages. Patients should not lie down for at least 30 minutes following alendronate intake.
Alendronate tablets should not be chewed or triturated.
Should a weekly dosage of MARVIL 70 be omitted, a tablet must be taken on the first morning after remembering. Do not take 2 tablets on the same day, but return to taking 1 tablet once a week, as originally scheduled, on the chosen day.

CONTRAINDICATIONS
Known hypersensitivity to the active principle or any component of this product or any other bisphosphonate. Abnormalities of the esophagus which may delay esophageal emptying such as stricture or achalasia. Inability to stand or sit upright for at least 30 minutes after the tablet intake. Severe hypocalcemia. Severe renal insufficiency.

WARNINGS
Like other bisphosphonates, alendronate may cause local irritation of the upper gastrointestinal mucosa.
Some patients receiving alendronate treatment experienced adverse events such as esophagitis, esophageal ulcers and erosions, occasionally with bleeding and rarely followed by esophagic stricture. Due to the severity of these events, physicians should instruct their patients to discontinue MARVIL 70 treatment and seek medical assistance in presence of any sign or symptom indicating any possible esophagic adverse reaction (dysphagia, odynophagia, retrosternal pain or heartburn that is new or worsens).
The risk of developing esophagic adverse events seems to be greater in those patients who lie down immediately after taking alendronate, who swallow it with a small quantity of water or who continue to take it even after the onset of signs indicating esophagic irritation. Therefore, it is very important that the patients follow the dosing instructions. Patients who cannot comply with these instructions due to mental disability, should follow MARVIL 70 treatment under strict supervision.

PRECAUTIONS
MARVIL 70 is not recommended for patients with severe renal insufficiency due to lack of clinical data.
Like other bisphosphonates, MARVIL 70 should be administered with precaution in patients with gastrointestinal problems such as dysphagia, symptomatic esophageal disease, gastritis, duodenitis and gastric or duodenal ulcers.
The disturbances of calcium metabolism such as vitamin D deficiency and hypocalcemia should be treated completely before administering MARVIL 70 because, though infrequently, it may cause transient and asymptomatic decreases in serum calcium due to alendronate mechanism of action.

Interactions with other drugs
Simultaneous administration of MARVIL 70 with calcium-rich beverages or food, like milk and yogurt, is not recommended due to possible interference with MARVIL absorption. Sucralfate, a sequestering agent of biliary salts, and medications with high content of calcium (calcium supplements), iron, magnesium or aluminum, including antacids and multivitaminic preparations with minerals can also interfere with MARVIL 70 absorption and hence should not be administrated concomitantly but after a minimum interval of 30 minutes.
Concomitant administration with nonsteroidal anti-inflammatory drugs including aspirin may increase the risk of digestive mucous irritation.
Ranitidine IV administration doubles the bioavailability of oral alendronate. However, the clinical significance of this effect and whether similar increments will occur in those patients receiving oral H2 antagonists is unknown.
In healthy patients, oral prednisone (20 mg three times daily during five days) did not produce a significant clinical change in the bioavailability of oral alendronate (mean increase was 20% to 44%).

Carcinogenesis, tumorigenesis, mutagenesis
In 2-year carcinogenicity studies in mice and rats receiving alendronate at doses equivalent to 1 and 1,2 times the maximum recommended daily dose of 40 mg for humans, based on body surface area, an increased number of parafollicular cell (thyroid) adenomas was reported in male rats and of retro-orbital gland adenomas (not present in humans) in female mice with respect to controls. The importance of these findings in humans is not known.
Alendronate did not produce genotoxicity in specific essays (*in vitro* microbial mutagenesis assay with and without metabolic activation, *in vitro* mammalian cell mutagenesis assay, *in vitro* alkaline elution assay in rat hepatocytes and in vivo chromosomal aberrations in mice). However, an *in vitro* chromosomal aberration assay in ovarian cells of Chinese hamster showed ambiguous results. Alendronate did not produce effects on the fertility of male and female rats with oral doses equivalent to 1,3 times the 40mg human daily dose calculated according to body surface area.

Reproduction
Reproduction studies in rats receiving alendronate doses up to 2,6 times the maximum recommended 40mg human daily dose, based on body surface area, evidenced a decreased survival postimplantation and a decreased body weight gain in born pups. The number of incomplete fetal ossification sites was higher than expected in vertebral, skull and sternebral bones. In pregnant rats receiving alendronate doses equivalent to 3,9 times the maximum recommended 40mg human daily dose, based on body surface area, maternal hypocalcemia and increased mortality were reported. Oral supplementation with calcium did not ameliorate hypocalcemia or prevent maternal deaths and neonatal deaths due to delayed delivery; meanwhile, intravenous calcium prevent maternal but not neonatal deaths.
No teratogenic effects were observed when pregnant rabbits were treated with high doses of alendronate.

Pregnancy
No studies have been performed in pregnant women. MARVIL 70 should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Lactation
It is unknown whether alendronate is excreted through human milk therefore caution should be taken when administering MARVIL 70 to nursing women.

Pediatric use
There is no available data on the efficacy and security of alendronate in children.

Geriatric use
No dosage adjustment is required for the elderly.

ADVERSE REACTIONS
Safety and tolerability profile of alendronate at one weekly dose of 70 mg is similar to that of continuous administration of alendronate 10 mg/day, both for 1 year, for the treatment of postmenopausal osteoporosis.
Adverse manifestations related to alendronate administration, in ≥ 1% of women that received either of the two treatments, classified as *frequent* (frequency >10%), *occasional* (between 1% to 10%) o *rare* (<1%), are the following:
• *Alendronate 70 mg/week (n=519):*
Occasional: abdominal pain, dyspepsia, acid regurgitation, nausea, abdominal distention, pain (bone, muscle or joint). *Rare:* constipation, flatulence, gastritis, gastric ulcer, muscle cramp.
• *Alendronate 10 mg/day (n=370):*
Occasional: abdominal pain, dyspepsia, acid regurgitation, nausea, abdominal distention, constipation, flatulence, gastritis, gastric ulcer, pain (bone, muscle or joint), muscle cramp.

Laboratory tests
In clinical studies, asymptomatic, mild and transient decreases in serum calcium and serum phosphate were reported in approximately 18% and 10% of patients, respectively. However, the incidences of reduction in serum calcium to < 8,0 mg/dL (2,0 mM) and in serum phosphate to ≤ 2,0 mg/dL (0,65 mM) were similar in both placebo and treatment groups.
In *pharmacosurvillance studies* with alendronate at different doses and for different indications, the following adverse reactions have been described:
General: hypersensitivity reactions including urticaria and rarely angioedema.
Gastrointestinal: esophagitis, esophagic erosion, esophagic ulcers, rarely esophageal stricture or perforation. Gastric and duodenal ulcers have also been reported, some severe and with complications.
Skin: rash (occasionally with photosensitivity).
Senses: rarely uveitis.

OVERDOSAGE
No specific data is available on the treatment of overdosage with MARVIL 70. Overdosage may cause hypocalcemia, hypophosphatemia and undesirable gastrointestinal reactions such as gastric pyrosis, esophagitis, gastritis or ulcers. Milk or antacids should be given to bind alendronate.
Due to risk of esophageal irritation, vomiting should not be induced and the patient should remain upright (standing or sitting upright). Dialysis is not beneficial.
In case of overdosage, medical advice should be sought at the nearest Hospital or Toxicology centers.

Recommended initial treatment for overdosage: after carefully evaluating the clinical status of the patient, the time passed since the ingestion, the amount of ingested toxicological doses, and the possible contraindications of the procedure, the medical professional should decide whether to prescribe the general rescue therapy.

INFORMATION FOR PATIENTS

LEAFLET FOR THE COMPREHENSION OF POSTMENOPAUSAL OSTEOPOROSIS AND ITS TREATMENT

Your physician has prescribed you **MARVIL 70** for the treatment of bone loss that usually initiates after menopause.
MARVIL 70 has been elaborated by researchers who have been studying bone metabolism and bone disorders for many years.
This leaflet will help you understand osteoporosis and will provide you with useful instructions in order to obtain better results from of this treatment.
Keep this leaflet with the **MARVIL 70** package and, should you have any further question or concern, do not hesitate to consult your doctor.

WHAT IS THE OSTEOPOROSIS?

The osteoporosis is a silent disease that produces no symptoms for many years. It is caused by a loss of bone components, leading to a slow but progressive increase of bone fragility that can result in fractures, either spontaneously or from minor injury, most usually in the spine, hip and wrist.
Tiny vertebra fractures over the time can cause height loss and eventually curve the spine. Osteoporosis is four times more frequent in women but can occur in men too.

POSTMENOPAUSAL OSTEOPOROSIS

Normally your bones are being rebuilt all the time. Over the years, the bone is almost totally restored by removal of old or disposable material (resorption process) and formation of new material instead (formation process). This process keeps the skeleton adaptable to the activity requirements of each person.
During human growth (first life stage) the amount of newly formed bone exceeds the amount of removed bone. Maximum bone density and strength is achieved during the second decade (20-25 years of age) and up to 40 years of age, bone formation and destruction rates are balanced in healthy subjects.
After this age, and especially in menopausal women, bone loss accelerates and predominates above bone formation due to progressive decay until natural disappearance of the hormones produced by the ovaries (estrogens). Thus, as from menopause, bone material becomes less dense and more fragile. This process is slow and asymptomatic until fractures occur. One out of 4 postmenopausal women is at risk of osteoporotic fractures.
Loss and progressive deterioration of bone may be prevented and treated, even when osteoporosis has already been established. Intervention measures may help recover bone strength and prevent the progression of the disease.

FACTORS THAT MAY INCREASE THE RISK OF OSTEOPOROSIS

Risk factors are Caucasian race, low body weight, small frame, family history of osteoporosis (mother, sisters, etc.), diet poor in calcium, sedentary habits, smoking, drinking alcohol, etc. Some of these risk factors can be corrected. Moreover, early menopause (menstruation cessation) may lead to premature imbalance of bone activity favoring bone loss. Some other diseases that induce bone loss and may cause osteoporosis should also be considered.

WHAT CAN MARVIL 70 DO FOR YOUR BONES?

MARVIL 70 IS A NON-HORMONAL MEDICINE INDICATED FOR POSTMENOPAUSAL OSTEOPOROSIS.
Clinical investigations evidenced that one-year-treatment with **MARVIL 70** not only stopped bone loss but also showed a significant bone mass increase in the whole skeleton.
Most of the osteoporotic patients that fully comply with **MARVIL 70** treatment will show a decreased risk of osteoporotic fractures of wrist, spine and hip, due to minimal injury, especially if treatment is initiated early. Moreover, these patients will have reduced possibilities of height decrease and curved spine. However, in order to ensure optimal results, treatment should be complemented with dairy products, lifestyle changes (low consumption of tobacco and alcohol) and physical exercise according to age.

WHAT SHOULD BE TAKEN INTO ACCOUNT FOR THE ADMINISTRATION OF MARVIL 70?

MARVIL 70 should be administered once weekly. To avoid omissions, it is recommended that you choose the most appropriate day of the week to take the medication comfortably.
For optimal administration of **MARVIL 70** and to avoid possible unwanted effects, the following instructions should be followed carefully:
MARVIL 70 tablet should be necessarily taken after an overnight fast, with a full glass of plain water, at least 30 to 60 minutes before breakfast. Mineral water with high calcium mineral content should not be used. After ingestion, patient should remain in upright position for 30 minutes, either sitting upright, standing or walking, avoiding lying down in bed.
MARVIL 70 tablet should be taken without any food or beverage such as milk, cheese, dairy products, tea, coffee, juice, antacids, calcium or vitamin supplements because they decrease alendronate absorption and, hence, its therapeutic action. Dairy products or calcium supplements should be taken as far as possible from **MARVIL 70** intake (2-3 hours).
MARVIL 70 tablets should not be chewed or triturated.
In case you miss one weekly dosage, you should take the tablet on the first morning after you remember, on an empty stomach, and then follow the treatment taking the tablet on the day chosen before the omission.
Upper gastrointestinal disturbances may occasionally occur among others (see Adverse Reactions in the Package Insert). In general, they occur during the first weeks of treatment, are transient and cede spontaneously. If this is not the case and you experience difficulty or pain upon swallowing or heartburn during treatment, you should suspend medication and immediately consult your doctor.
Your should tell your doctor whether you have a history of esophagus, stomach or bowels disorders, before initiating the treatment.
MARVIL 70 should not be administered to children, pregnant or nursing women, patients with a history of allergy to the product, upper gastrointestinal disorders such as esophagic stricture or achalasia, low serum calcium levels, severe chronic renal insufficiency or inability to stand or sit upright for 30 minutes.

FAVORABLE LIFESTYLE CHANGES

Physical exercise may exert a favorable influence on bone quality. Sedentary habits should be avoided; regular walking (at least 1 hour per day) and exercise are recommended.
If possible, sit, stand or run with your back upright. You should avoid falls and strikes and walk very carefully on slipping floors, especially of bathrooms and bathtub. Stairs should be well illuminated and small objects should not be left on the floor (toys, etc.). Do not use unstable or insecure devices to reach high places.
It is recommended that you moderate the consumption of meat, salt, alcohol, coffee and tobacco, and eat a balanced diet that
liters of milk per day (preferably skim), cheese and yogurt
calcium ingesta; fish and liver that are good sources of na
Vitamin D is very necessary for calcium metabolism but bec
with sunlight exposure; therefore, either moderate sunbathi
the open air during 30 to 60 minutes per day is recommend.

FINAL RECOMMENDATION

It is possible to prevent, stop or revert postmenopausal ost
treatment may be prolonged for some years but knowing th
fulfill it. Perseverance is required to experience treatmer
bones have to undergo their own renewal process. It is ver
you consult your doctor regularly and that you adopt a l
enable you to walk upright in the future and completely enjoy
Consult your doctor

"This medication was prescribed for your particular medic
not recommend it to other persons".

"KEEP OUT OF THE REACH OF CHILDREN"

Store **MARVIL 70** tablets at room temperature and away
direct light.

CORRECT INFORMATION FORMS PART OF THE MEDICINE

HOW SUPPLIED
Packages containing 2 and 4 coated tablets with 70 mg of alendronate

STORAGE CONDITIONS
Store between 15 - 30°C, protected from light.

"KEEP OUT OF THE REACH OF CHILDREN"

ELISIUM

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