Buffered Binosto®

Alendronate Sodium Trihydrate

Read package insert carefully before use.

Consult your doctor for more information.

Prescription medicine only. Keep out of reach of children.

1. NAME OF THE MEDICINAL PRODUCT

Buffered Binosto 70 mg effervescent tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 70mg alendronic acid as 91.37 mg of alendronate sodium trihydrate.

Excipients: Sodium dihydrogen citrate, Citric acid anhydrous, Sodium hydrogen carbonate, Sodium carbonate anhydrous, Strawberry flavour [Maltodextrin (Maize), Arabic gum, Propylene glycol (E 1520), nature-identical flavouring substances], Acesulfame potassium, Sucralose.

Each effervescent tablet contains 602,54mg of sodium.

3. PHARMACEUTICAL FORM

Effervescent Tablet

White to off-white round effervescent tablets of 25 mm diameter, flat faced with bevelled edges. After dissolution the solution has a pH of 4.8-5.4

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Buffered Binosto is indicated for the treatment of : osteoporosis in postmenopausal women. Osteoporosis may be confirmed by finding of low bone mass (for example, at least 2 standard deviations below the pre-menopausal mean) or by the presence or history of osteoporotic fracture.

4.2 Posology and method of administration

Posology

The recommended dose is one 70mg effervescent tablet once weekly.

Patient should be instructed that if they miss a dose of Alendronate sodium trihydrate (Buffered Binosto) 70 mg, they should take one effervescent tablet on the morning after they remember. They should not take two effervescent tablets on the same day but should return to taking one effervescent tablet once a week, as originally scheduled on their chosen day.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of

Alendronate sodium trihydrate (Buffered Binosto) on an individual patient basis, particularly after 5 or more years of use.

Paediatric population
Alendronate sodium trihydrate (Buffered Binosto) is not recommended for use in children under the age of 18 years due to insufficient data on safety and efficacy in conditions associated with paediatric osteoporosis (also see section 5.1).

Use in the elderly
In clinical studies there was no age related difference in the efficacy or safety profiles of alendronate. Therefore no dosage adjustment is necessary for the elderly.

Use in renal impairment :
No dosage adjustment is necessary for patients with GFR greater than 35 ml/min. Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, due to lack of experience.

Method of administration

To permit adequate absorption of alendronate :
Alendronate sodium trihydrate (Buffered Binosto) 70 mg must be taken at least 30 minutes before the first food, beverage or medicinal product of the day with plain water only. Other beverages (including mineral water), food and some medicinal products are likely to reduce the absorption of alendronate (see section 4.5)

To facilitate delivery to the stomach and thus reduce the potential for local and oesophageal irritation/adverse experiences (see section 4.4):

- Alendronate sodium trihydrate (Buffered Binosto) 70 mg should only be taken upon arising for the day dissolved in half a glass of plain water (not less than 120 ml or 4.2 fl.oz.). Dissolving the tablet in water yields a buffered solution of pH 4.8 – 5.4. The buffered solution should be drunk, once the fizzing has subsided and the effervescent tablet has completely dissolved to give a clear, to slightly cloudy, buffered solution, followed by at least 30ml (one sixth of a glass) of plain water. Additional plain water may be taken.
- **Patients should not swallow the undissolved effervescent tablet, should not chew the effervescent tablet or allow the effervescent tablet to disaolve in their mouths because of the risk for oropharyngeal irritation (see section 4.4 and 4.8)**
- If the table does not dissolve completely, the buffered solution may be stirred until it is clear to slightly cloudy.
- Patients should not lie down until after their first food of the day, which should be at least 30 minutes after drinking the oral solution.
- Patients should not lie down for at least 30 minutes after drinking the oral solution
- Alendronate sodium trihydrate (Buffered Binosto) 70 mg should not be taken at bedtime or before arising for the day.
- Alendronate sodium trihydrate (Buffered Binosto) 70 mg can be given to patients who are unable or unwilling to swallow tablets.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see section 4.4)

Alendronate sodium trihydrate (Buffered Binosto) 70 mg has not been investigated in the treatment of glucocorticoid-induced osteoporosis.

4.3 Contraindications

- Hypersensitivity to alendronate or to any of the excipients listed in section 6.1.
- Abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 30 minutes.
- Hypocalcaemia
- See also section 4.4.

4.4 Special warnings and precautions for use

Alendronate can cause local irritation of the upper gastro-intestinal mucosa. Because there is a potential for worsening of the underlying disease, caution should be used when alendronate is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (1 year) of major gastro-intestinal disease such as peptic ulcer, or active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract other than pyloroplasty (see section 4.3). In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

Oesophageal reactions (sometimes severe and requiring hospitalisation), such as oesophagitis, oesophageal erosions and oesophageal ulcers, rarely followed by oeshophageal stricture, have been reported in patients receiving alendronate. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontainue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain, new or worsening heartburn.

The risk of severe oesophageal adverse experiences appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate after developing symptoms suggestive of oesophageal irritation. It is very important that the full dosing instructions are provided to, and understood by the patient (see section 4.2). Patients should be informed that failure to follow these instructions may increase the risk of oesophageal problems.

While no increased risk was observed in extensive clinical trial sconducted with alendronate tablets, there have been rare (post-marketing) reports of gastric and duodenal ulcers,some severe and with complications.

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

The following risk factors should be considered when evaluating an individual's risk of developing osteonecrosis of the jaw:

- potency of the bisphosphonate (highest for zoledronic acid), route of administration (see above) and cumulative dose
- cancer, chemotherapy, radiotherapy, corticosteroids, smoking

- a history of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures and poorly fitting dentures.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with poor dental status.

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.
Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.
During bisphosphonate treatment, all patient should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain or swelling.

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been severe and/or incapacitating (see section 4.8). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Atypical fracture of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-terms treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

In post-marketing experience of alendronate, there have been rare reports of severe skin reactions including Steven Johnson syndrome and toxic epidermal necrolysis.

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Alendronate is not recommended for patients with renal impairment where GFR is less than 35 ml/min, (see section 4.2).

Paediatric population

Alendronate sodium trihydrate (Buffered Binosto) is not recommended for use in children under the age of 18 years due to insufficient data on safety and efficacy in conditions associated with paediatric osteoporosis (also see section 4.2 and 5.1).

Causes of osteoporosis other than oestrogen deficiency and ageing or glucocorticoid use should be considered.

Hypocalcaemia must be corrected before initiating therapy with alendronate (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting Alendronate sodium trihydrate (Buffered Binosto) treatment. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with Alendronate sodium trihydrate (Buffered Binosto) 70 mg.

Due to the positive effects of alendronate in increasing bone mineral, decrease in serum calcium and phosphate may occur especially in patients taking glucocorticoids in whom calcium absorption may be decreased. These are usually small and asymptomatic. However,there have been rare reports of symptomatic hypocalcemia, which have occasionally been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption).

Ensuring adequate calcium and vitamin D intake is particularly important in patients receiving glucocorticoids.

Excipients

This medicinal product contains 26.2 mmol (or 602.54 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet

4.5 Interaction with other medicinal products and other forms of interaction

If taken at the same time, it is likely that food and beverages (including mineral water), calcium supplements, antacids, and some oral medicinal products will interfere with absorption of alendronate. Therefore, patient must wait at least 30 minutes after taking alendronate before taking any other oral medicinal product (see section 4.2 and 5.2)

In healthy subjects, oral prednisone (20 mg there times daily for five days) did not produce a clinically meaningful change in oral bioavailability of alendronate (a mean increase ranging from 20% to 44%).

No other interactions with medicinal products of clinical significance are anticipated. A number of patients in the clinical trials received oestrogen (intravaginal, transdermal, or oral) while taking alendronate. No adverse experiences attributable to their concomitant use were identified.

Since NSID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.

Although otherwise specific interaction studies were nor performed, in clinical studies alendronate was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of clinical adverse interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
Alendronate should not be used during pregnancy. There are no adequate data from the use of alendronate in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, or postnatal development. Alendronate given during pregnancy in rats caused dystocia related to hypocalcemia (see section 5.3)

Breastfeeding

It is unknown whether alendronate is excreted into human breast milk. Given the indication, alendronate should not be used by breast-feeding women

Fertility
Bisphosphonates are incorporated into the bone matrix, from which the are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use (see section 5.2). There are no data on fetal risk in humans. However, there is a theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on the risk has not been studied.

4.7 Effects an ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, certain adverse reactions that have been reported with alendronate may affect some patients' ability to drive or operate machinery. Individual responses to alendronate may vary (see section 4.8).

4.8 Undesirable effects

In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of alendronate 70 mg once weekly (n=519) and alendronate 10 mg/day (n=370) were similar.

In two three-year studies of virtually identical design, in post-menopausal women (alendronate 10 mg: n=196, placebo: n=397) the overall safety profiles of alendronate 10 mg/day and placebo were similar.

Adverse reactions reported by the investigators as possibly, probably or definitely drug-related are presented below if they occurred in ≥ 1% in either treatment group in the one-year study, or in ≥ 1% of patients treated with alendronate 10 mg/day and at a greater incidence than in patients given placebo in the three-years studies :

	ONE-YEAR STUDY		**THREE-YEAR STUDIES**	
	alendronate Once Weekly 70 mg (n=519) %	alendronate 10 mg/day (n=370) %	alendronate 10 mg/day (n=196) %	placebo (n=397) %
Gastro-intestinal				
abdominal pain	3.7	3.0	6.6	4.8
dyspepsia	2.7	2.2	3.6	3.5
acid regurgitation	1.9	2.4	2.0	4.3
nausea	1.9	2.4	3.6	4.0
abdominal distension	1.0	1.4	1.0	0.8
constipation	0.8	1.6	3.1	1.8
diarrhoea	0.6	0.5	3.1	1.8
dysphagia	0.4	0.5	1.0	0.0
flatulence	0.4	1.6	2.6	0.5

gastritis	0.2	1.1	0.5	1.3
gastritic ulcer	0.0	1.1	0.0	0.0
oesophageal ulcer	0.0	0.0	1.5	0.0
Musculoskeletal				
musculoskeletal pain (bone, muscle or joint)	2.9	3.2	4.1	2.5
muscle cramp	0.2	1.1	0.0	1.0
Neurological				
headache	0.4	0.3	2.6	1.5

The following adverse reactions have been reported during clinical studies and/or post-marketing useof oral alendronate tablets:

	Adverse reactions				
	Very Common (≥ 1/10)	**Common** (≥ 1/100, <1/10)	**Uncommon** (≥ 1/1,000, <1/100)	**Rare** (≥ 1/10,000, <1/1,000)	**Very Rare** (<1/10,000)
Immune system disorders				Hypersensitivity reactions including urticaria and angioedema	
Metabo-lism and nutrition disorder				Symptomatic hypocalcaemia, often in association with predisposing conditions [#].	
Nervous system disorders		headache, dizziness[§]	dysgeusia[§]		
Eye disorders			eye inflammation (uveitis, scleritis, episcleritis)		
Ear and labyrinth disorders		vertigo[§]			
[‡]Gastro-intestinal disorders		abdominal pain, dyspepsia, constipa-tion, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation	nausea,vomiting, gastritis, oesopha-gitis*, oesophageal erosions*, melena[§]	oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestion*, PUBs (perforation, ulcers, bleeding)[#]	

Skin and subcutaneous tissue disorders		alopecia[§] , pruritus[§]	rash, erythema	rash with photosensitivity severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis[+]	
Musculoskeletal, connective tissue and bone disorders :	musculoskeletal (bone, muscle or joint) pain, which is sometimes severe [#§]	joint swelling[§]		Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction) [#] Osteonecrosis of the jaw[§+], stress fractures of the proximal femoral shaft[§+]	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
General disorders and administration site condition		asthenia[§], peripheral oedema[§]	transient symptoms as in an acute-phase response (myalgia, malaise and rarely, fever typically in association with initiation of treatment[§].		

[#]*See section 4.4*

[§]*Frequency in Clinical Trials was similar in the drug and placebo group*

[*]*See sections 4.2 and 4.4*

[+]*This adverse reactions was identified through post-marketing surveillance. The frequency of rare was estimated based on relevant clinical trials*

‡These adverse reactions were identified with the tablet form, and may not all apply to Alendronate sodium trihydrate (Buffered Binosto) 70 mg, which is taken as a buffered oral solution.

Reporting of suspected adverse reactions

Inform healthcare professionals about these unexpected effect when using drug.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are

asked to report any suspected adverse reactions to local safety authority or marketing authorization holder

4.9 Overdose

Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage.

No specific information is available on the treatment of overdosage with alendronate. Milk or antacids should be given to bind alendronate. Owing to the risk of oeshophageal irritation, vormiting should not be induced and the patient should remain fully upright.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Drugs affecting bone structure and mineralisation, bisphosphonates
ATC Code: M05B A04

The active ingredient of Alendronate sodium trihydrate (Buffered Binosto) 70 mg, alendronate sodium trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation.
Preclinical studies have shown preferential localisation of alendronate to sites of active resorption. Activity of osteoclasts is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronate is of normal quality.

Oesophageal toxicity associated with alendronate treatment is a multifactorial effect the seems predominately medicated by local irritations of the oesophageal mucosa through crystalline matter, which is also known as pill oesophagitis. Gastroesophageal acid reflux might be a concomitant factor, as acid blockage is one of the main treatments once alendronate-associated oesophagitis occurs. Alendronate sodium (Buffered Binosto) 70 mg effervescent tablet administered as a buffered solution was designed to fully solubilise alendronate in a drinkable solution of high pH with acing neutralising capacity, to minimise particulate alendronate from contacting the mucosa and to prevent strong stomach acid being present in the stomach, diminishing damage potential in cases of oesophageal reflux. Refer to section 4.8 for postmarketing data retrieved from the US.

Treatment of post-menopausal osteoporosis
Osteoporosis is defined as BMD of the spine or hip 2,5 SD below the mean value of a normal young population or as a previous fragility fracture, irrespective of BMD.

The therapeutic equivalence of alendronate 70 mg once weekly (n=519) and alendronate 10 mg daily (n=370) was demonstrated in a one-year multicentre study of post-menopausal women with osteoporosis.

The mean increases from baseline in lumbar spine BMD at one year were 5.1% (95% Cl: 4.8, 5.4%) in the 70 mg once-weekly group and 5.4% (95% Cl: 5.0, 5.8%) in the 10 mg daily group. The mean BMD increases were 2.3% and 2.9% at the femoral neck and 2.9% and 3.1% at the total hip on the 70 mg once

weekly and 10 mg daily groups, respectively. The two treatment groups were also similar with regard to BMD increases at other skeletal sites.

The effects of alendronate on bone mass and fracture incidence in post-menopausal women were examined in two initial efficacy studies of identical design (n=994) as well as in the Fracture Intervention Trial (FIT: n=6,459)

In the initial efficacy studies, the mean bone mineral density (BMD) increases with alendronate 10mg/day relative to placebo at three years were 8.8%, 5.9% and 7.8% at the spine, femoral neck and trochanter, respectively. Total body BMD also increased significantly. There was a 48% reduction (alendronate 3.2% vs placebo 6.2%) in the proportion of patients treated with alendronate experiencing one or more vertebral fractures relative to those treated with placebo. In the two-year extension of these studies BMD at the spine and trochanter continued to increase and BMD at the femoral neck and total body were maintained.
FIT consisted of two placebo-controlled studies using alendronate daily (5 mg daily two years and 10 mg daily for either one or two additional years):

- FIT 1: A three-year study of 2,027 patients who had at least one baseline vertebral (compression) fracture. In this study alendronate daily reduced the incidence of ≥ 1 new vertebral fracture by 47% (alendronate 7.9% vs. placebo 15.0%). In addition, a statistically significant reduction was found in the incidence of hip fractures (1.1% vs. 2.2%, a reduction of 51%).
- FIT 2: A four-year study of 4,432 patients with low bone mass but without a baseline vertebral fracture. In this study, a significant difference was observed in the analysis of the subgroup of osteoporotic women (37% of the global population who correspond with the above definition of osteoporosis) in the incidence of ≥ 1 vertebral fracture (2.9% vs. 5.8%, a reduction of 50%) and in the incidence of hip fractures (alendronate 1.0% vs. placebo 2.2%, a reduction of 56%).

Clinical efficacy of Alendronate sodium trihydrate (Buffered Binosto)70mg effervescent tablets for oral solution

BC-118-07: A clinical study with Alendronate sodium trihydrate (Buffered Binosto)70mg performed in 12 healthy female subjects. This clinical study evaluated gastric empty and gastric pH after administration of a conventional tablet and Alendronate sodium trihydrate (Buffered Binosto) 70 mg, effervescent tablet, with a high buffering capacity. The buffered solution has the potential for improving gastric tolerance. Both formulations tested, rapidly cleared the oesophagus and there were no statistically significant or physiologically relevant differences in gastric emptying times.
Mucosal exposure to alendronate at a pH less than 3 is irritating to gastro-oesophageal tissue. Ingestion of a conventional tablet resulted in alendronate being present in the stomach at a pH below 3 within minutes.
After dosing with Alendronate sodium trihydrate (Buffered Binosto) 70mg, the gastric pH generally increased to approximately 5 and remained at a plateau for 30 minutes then gradually decreased. The time taken for the gastric pH to drop below 3, after the ingestion of the medications was significantly higher with the effervescent tablets, in comparisons to the conventional tablet.
Therefore, Alendronate sodium trihydrate (Buffered Binosto) 70 mg minimises the possibility of exposing the oesophagus (in case of reflux) and the stomach to acidified alendronate.

Laboratory test findings
In clinical studies, asymptomatic, mild and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking alendronate 10 mg/day versus approximately 12 and 3% of those taking placebo.

However, the incidences of decreases in serum calcium to < 8.0 mg/dl (2.0 mmol/l) and serum phosphateto ≤ 2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

Paediatric population
Alendronate sodium trihydrate (Buffered Binosto) has been studied in a small number of patients with osteogenesisimperfecta under the age of 18 years. Results are insufficient to support the use of alendronate sodium trihydrate (Buffered Binosto) in paediatric patients with osteogenesisimperfecta.

5.2 Pharmacokinetic properties

Absorption

Relative to an intravenous reference dose, the oral mean bioavalibility of alendronate tablets in women was 0.64% for doses ranging from 5 to 70 mg when administered after and two hours before a standardised breakfast. Bioavailability was decreased similarly to an estimated 0.46% and 0.39% when alendronate was administered one hour or half an hour before a standardised breakfast.

The bioavalibility of Alendronate sodium trihydrate (Buffered Binosto) 70 mg effervescent tablets is equivalent to that of alendronate tablets, but the intraindividual variation in excretion (and therefore in absorption) is smaller for the effervescent tablets (CV 32.0 vs 42.1% cumulative excretion in the first 48 hours, CV 37.5 vs 45.6% maximum excretion rate).

In osteoporosis studies, alendronate was effective when administered at least 30 minutes before the first food or beverage of the day.

Bioavailibility was negligible whether alendronate was administered with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

Distribution

Studies in rats show that alendronate transiently distributes to soft tissue following 1mg/kg intravenous administration but is then rapidly redistributed to bone or excreated in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 liters in humans. Concentrations of drug in plasma following therapeutic oral doses are too low for analytical detection (<5 ng/ml). Protein binding in human plasma is approximately 78%.

Biotransformation

There is no evidence that alendronate is metabolised in animals or humans.

Elimination

Following a single intravenous dose of [^{14}C] alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the faeces.
Following a single 10 mg intravenous dose, the renal clearance of alendronate was 71 ml/min, and systemic clearance did not exceed 200 ml/min.
Plasma concentrations fell by more than 95% within six hours following intravenous administration.
The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronate

from the skeleton. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other medicinal products by those systems in humans.

Characteristics in patients

Preclinical studies show that the drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after chronic dosing with cumulative intravenous doses up to 35 mg/kg in animals. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
Studies in rats have shown that treatment with alendronate during pregnancy was associated with dystocia in dams during parturition, which was related to hypocalcaemia.
In studies, rats given high doses showed an increased incidence of incomplete foetal ossification. The relevance to humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen citrate
Citric acid anhydrous
Sodium hydrogen carbonate
Sodium carbonate anhydrous
Strawbery flavour [Maltodextrin (Maize), Arabic gum, Propylene glycol (E 1520, nature-identical flavouring substance]
Acesulfame potassium
Sucralose

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years

6.4 Special precautions for storage

Store at temperatures not exceeding 30°C.Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

The effervescent tablets are provided in strips of composite foil (paper / polyethylene / aluminium / Zn-ionomer), with 2 effervescent tablets packed in individual units per strip.

Packs with 4 or 12 effervescent tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The appearance of the product after dissolution is a clear to slightly cloudy solution.

7. MARKETING AUTHORISATION HOLDER

Registrated in Indonesian by : PT. Pyridam Farma, Tbk, Jakarta Indonesia

8. MARKETING AUTORISATION NUMBER (S)

Registration number in Indonesia : DKI1951700211A1

9. Manufacturer information

NAME AND ADDRESS OF MANUFACTURER

SwissCo Services AG

Bahnhofstrasse 14, CH-4334 Sisseln, Switzerland

10. DATE OF REVISION OF THE TEXT

09 December 2015

HARUS DENGAN RESEP DOKTER

Buffered Binosto® 70 mg effervescent tablets

Natrium Alendronate Trihidrat

Informasi Produk untuk Pasien

Apa yang ada di brosur ini?

Brosur ini akan menjawab beberapa pertanyaan umum tentang Binosto

Brosur ini tidak mencakup keseluruhan informasi yang lengkap. Jika Anda ingin tahu lebih lanjut, berkonsultasilah kepada Dokter Anda atau Apoteker.

Semua obat memiliki risiko dan manfaat. Dokter Anda telah menimbang segala risiko dengan manfaat yang diharapkan dari penggunaan obat ini.

Jika Anda ragu dalam menggunakan obat ini, berkonsultasilah kepada Dokter Anda atau Apoteker.

Simpan brosur ini.

Untuk apa Binosto digunakan?

Obat ini digunakan untuk:

Pengobatan Osteoporosis pada Wanita postmenopausal. Osteoporosis yang dikonfirmasikan dengan adanya kepadatan tulang yang rendah (sebagai contoh, setidaknya 2 standar deviasi berada dibawah pre-menopausal yang berarti) atau adanya riwayat dari fraktur osteoporosis.

Tanyakan Dokter Anda, mengapa obat ini diberikan untuk Anda.

Sebelum Anda menggunakan Binosto

Kapan Anda tidak boleh menggunakannya

Jangan gunakan obat ini jika Anda:

- Hipersensitif terhadap alendronate atau terhadap salah satu eksipien yang terkandung dalam obat ini
- Kelainan kerongkongan dan faktor-faktor lain yang menunda esofagus mengosongkan seperti striktur atau akalasia.
- Ketidakmampuan untuk berdiri atau duduk tegak selama minimal 30 menit.
- Hipokalsemia
- Femur atypical fraktur
- Pasien dengan gangguan ginjal di mana GFR kurang dari 35 ml / menit
- Anak di bawah usia 18 tahun

Gunakan obat ini dengan perhatian khusus jika Anda:

- Pasien dengan esophagus *Barret*
- Pasien yang sedang dalam diet kontrol natrium

Jangan gunakan obat ini setelah tanggal kadaluarsa yang tercantum pada kemasan atau jika kemasan robek atau jika kemasan dalam kondisi tidak bagus.

Jika Anda tidak yakin apakah Anda harus mulai menggunakan obat ini, berkonsultasilah kepada Dokter Anda.

Sebelum Anda mulai menggunakannya

Beritahukan kepada Dokter Anda jika Anda memiliki kondisi alergi terhadap obat lain, makanan, pengawet, atau pewarna.

Beritahukan Dokter atau apoteker Anda sebelum menggunakan Binosto jika Anda memiliki masalah ginjal, masalah dalam menelan atau pencernaan, dinyatakan Barret's oesophagus, kadar kalsium dalam darah rendah, masalah kesehatan gigi, menderita kanker, menjalani kemoterapi atau radioterapi, mengkonsumsi kortikosteroid seperti prednisone, perokok.

Sebelum menggunakan obat, Anda disarankan untuk memeriksa kesehatan gigi.

Beritahukan Dokter Anda jika Anda sedang hamil atau berencana untuk hamil.

Dokter Anda dapat berdiskusi dengan Anda tentang risiko dan manfaat dari penggunaan obat ini.

Beritahukan Dokter Anda jika Anda sedang menyusui.

Dokter Anda dapat berdiskusi dengan Anda tentang risiko dan manfaat dari penggunaan obat ini.

Jika Anda belum memberitahukan Dokter Anda tentang kondisi di atas, beritahukan Dokter Anda sebelum Anda diberikan obat ini.

Penggunaan obat-obat lainnya

Jika diminum pada saat yang bersamaan, ada kemungkinan bahwa makanan dan minuman (termasuk air mineral), suplemen kalsium, antasid, dan beberapa produk obat oral akan mengganggu penyerapan alendronate. Oleh karena itu, pasien harus menunggu setidaknya 30 menit setelah minum alendronate sebelum mengambil obat oral lainnya Anda mungkin disarankan untuk mengkonsumsi suplemen kalsium dan vitamin D, jika dirasa tidak cukup diperoleh dari makanan.

Monitoring asupan kadar kalsium dan vitamin D mungkin dibutuhkan jika Anda menerima pengobatan glucocorticoids.

Penggunaan NSAID dapat menyebabkan iritasi saluran cerna, untuk itu hati-hati ketika menggunakan Bersama dengan obat ini.

Beritahukan Dokter atau Apoteker Anda jika Anda menggunakan obat-obat lainnya, termasuk obat tanpa resep dari Dokter.

Bagaimana menggunakan Binosto

Ikuti semua petunjuk yang diberikan oleh Dokter Anda dengan hati-hati

Buffered Binosto dilarutkan dalam sejumlah air (tidak kurang dari 120 ml). Segera minum larutan seketika gelembung hilang dan tablet secara sempurna larut, kemudian minum air putih setidaknya satu per enam gelas.

Buffered Binosto diminum pada pagi hari, Pasien tidak boleh berbaring, tidak boleh makan, minum atau menggunakan obat-obatan lainnya selama 30 menit setelah Buffered Binosto diminum. Anda tidak boleh berbaring sampai Anda mengkonsumsi makanan pertama.

Pasien tidak boleh menelan tablet effervescent Buffered Binosto secara utuh, tidak boleh dikunyah atau terlarut dalam mulut.

Buffered Binosto hanya dilarutkan menggunakan *plain water only* (bukan mineral water atau air dengan rasa)

Berapa jumlah yang digunakan?

Dokter Anda akan menentukan dosis yang tepat untuk digunakan, tergantung kondisi kesehatan Anda.

Berapa lama menggunakannya?

Dokter Anda akan memberitahukan seberapa sering Anda membutuhkan pengobatan dengan obat ini.

Jika Anda menggunakan Buffered Binosto melebihi dari jumlah yang seharusnya?

Jika Anda menggunakan tablet effervescent berlebihan secara tidak sengaja, segera minum segelas penuh susu dan hubungi Dokter Anda. Jangan paksa Anda untuk muntah dan jangan berbaring.

Jika Anda lupa mengkonsumsi Buffered Binosto?

Jika Anda lupa mengonsumsi Alendronate sodium (Buffered Binosto) 70 mg, Anda harus mengonsumsi satu tablet effervescent pada pagi hari setelah Anda ingat. Jangan mengonsumsi dua tablet effervescent di hari yang sama. Kembali konsumsi satu tablet effervescent sekali sehari, sesuai dengan yang dijadwalkan sebelumnya.

Selama Anda menggunakan Binosto

Hal-hal yang harus Anda lakukan

Jika Anda akan menggunakan obat baru lainnya, beritahukan Dokter Anda atau Apoteker bahwa Anda menggunakan Binosto

Beritahukan Dokter lainnya, Dokter gigi, dan Apoteker yang mengobati Anda jika Anda sedang menggunakan Binosto

Jika Anda akan menjalani operasi, beritahukan ahli bedah atau ahli obat bius bahwa Anda menggunakan Binosto.

Jika Anda menjadi hamil selama menggunakan obat ini, segera beritahukan Dokter Anda.

Simpan semua jadwal temu dengan Dokter Anda supaya perkembangan Anda dapat diperiksa.

Efek Samping

Segera beritahukan Dokter Anda atau apoteker jika Anda merasa tidak nyaman ketika menggunakan obat ini.

Semua obat memiliki efek samping. Kadang-kadang efeknya serius, kebanyakan tidak. Anda mungkin membutuhkan perhatian medis jika Anda mengalami beberapa efek samping dari obat ini.

Jangan kuatir dengan daftar efek samping di bawah ini. Anda mungkin tidak mengalami efek-efek samping tersebut.

Sangat umum (*Very common*): nyeri musculoskeletal (tulang, otot atau sendi), yang terkadang bisa parah.

Umum (*Common*): sakit kepala, pusing, vertigo, sakit bagian perut, dyspepsia, konstipasi, diare, perut kembung, ulkus esofagus, dysphagia, distensi perut, regurgitasi asam, kebotakan, pruritus, pembengkakan sendi, lemas, edema pada jaringan.

Luar biasa (*Uncommon*): dysgeusia, inflamasi pada mata (uveitis, scleritis, episcleritis), mual, muntah, gastritis, esophagitis, pengikisan esofagus, melena, rash, erythema, gejala transisi sebagai respon fase akut (myalgia, malaise dan demam) yang biasanya terjadi dalam penggabungan dari treatment inisiasi.

Jarang terjadi (*Rare*): Reaksi hipersensitif meliputi urticaria, dan angioedema, symptomatic hypocalcaemia, sering dikaitkan dengan kondisi predisposisi, oesophageal stricture, oropharyngeal ulceration, upper gastrointestinal PUBs (perforasi, ulkus, pendarahan), kemerahan dengan, fotosensitifitas, reaksi parah pada kulit meliputi Stevens-Johnson syndrome, dan toxic epidermal necrolysis, atypical subtrochanteric dan diaphyseal femoral fractures (reaksi efek samping kelas bisphosphonate), osteonecrosis of the jaw, stress fractures dari poros proximal femoral.

Sangat Jarang terjadi (*Very Rare*): Osteonecrosis dari kanal external auditory (reaksi efek samping dari kelas bisphosphonate)

Deskripsi Produk

Komposisi

Binosto mengandung 91.37 mg natrium alendronate trihidrat setara dengan 70 mg asam alendronic

Kondisi Penyimpanan
Simpan pada suhu tidak lebih dari 30°C

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HARUS DENGAN RESEP DOKTER