

## Summary of Product Characteristics

### 1 NAME OF THE MEDICINAL PRODUCT

Teboneva 70mg Tablets and 1 microgram capsules, soft.

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 70 mg alendronic acid (as alendronate monosodium monohydrate).

Each capsule, soft contains 1 microgram alfacalcidol.

Excipients with known effect: One capsule, soft contains 98.8mg arachis oil (peanut oil), 1.144mg ethanol anhydrous and 7.88 mg mannitol–sorbitol–sorbitan–higher polyol mixture.

For the full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Tablet and capsule, soft

Tablet: white to off-white, round tablet, flat on both sides and with bevelled edges, stamped with “T” on one side and without marking on the other side.

Capsule, soft: opaque, white to off white oval capsule, soft, imprinted with “1.0” in black ink.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic Indications

Treatment of postmenopausal osteoporosis. Alendronic acid reduces the risk of vertebral and hip fractures.

#### 4.2 Posology and method of administration

Teboneva consists of two individual formulations: a tablet containing alendronic acid taken once weekly and a capsule containing alfacalcidol taken once daily. The dosage and method of administration for both formulations must be observed.

Patients should receive supplemental calcium if supply via dietary means is inadequate (see section 4.4).

##### Directions for ensuring adequate absorption of alendronic acid:

Alendronic acid 70 mg tablets should be taken once weekly in the morning, with plain water only and at least 30 minutes before the first intake of food, beverages or medicinal products for the day. Other beverages, including mineral water, food and some medicinal products are likely to impair the absorption of alendronic acid (see section 4.5).

The following directions should be observed, so that the tablets are delivered to the stomach as quickly as possible, thereby reducing the possibility of local and oesophageal irritation and/or undesirable effects (see section 4.4):

- Alendronic acid 70 mg tablets should be swallowed only after rising for the day, with a full glass of water (at least 200 ml).
- Patients should not chew the tablet or allow it to dissolve in their mouth, as there is a risk that oropharyngeal ulcers may develop.
- After taking alendronic acid 70 mg tablets, patients must not lie down for at least 30 minutes.
- The first food of the day must not be consumed within at least 30 minutes of taking the tablet.
- Alendronic acid 70 mg tablets must not be taken at bedtime or before firstly arising for the 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 Teboneva on an individual patient basis, particularly after 5 or more years of use.

*Use in the elderly:* in clinical studies, there was no age related difference in the efficacy or safety profile of alendronic acid. Thus, no dose adjustment is required for the elderly.

*Use in renal impairment:* no dose adjustment is required for patients with a glomerular filtration rate (GFR) above 35 ml/min. Alendronic acid is not recommended for patients with impaired renal function and a GFR below 35 ml/min, as experience is lacking.

Alendronic acid 70 mg tablets have not been investigated for the treatment of glucocorticoid-induced osteoporosis.

*Paediatric population:* alendronic acid 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).

#### Alfacalcidol capsules, soft:

Alfacalcidol capsules should be taken in the evening.

The recommended dosage is 1 µg per day. During therapy, serum calcium concentrations should be monitored and, if levels are high ( $> 2.6$  mmol/l), it must be ascertained whether additional agents containing calcium are being taken. If this is the case, these agents must be discontinued. If this is not possible, intake of alfacalcidol capsules must be suspended until serum calcium concentrations revert to normal (2.2–2.6 mmol/l).

The capsules should be swallowed whole with a sufficient amount of liquid. The doctor should individually decide on the duration of treatment for each patient.

Intake of Teboneva must be discontinued if either of the formulations is unsuitable for the patient.

Both components of Teboneva, alendronic acid and alfacalcidol, may exert opposite effects to avoid major fluctuations in serum calcium concentrations. Both substances can influence calcium concentrations in the blood: alendronic acid can reduce them, whilst alfacalcidol can increase them. The treating doctor should take this into account.

Due to the nature of the pathological process in osteoporosis, Teboneva is intended for long-term use. The duration of treatment depends on osteoporotic fracture risk; your doctor will decide for how long you will need to take Teboneva.

Teboneva is contraindicated in children and adolescents.

### 4.3 Contraindications

- Hypersensitivity to alendronic acid, alfacalcidol or to peanut (arachis) oil or to any of the excipients listed in section 6
- Oesophageal abnormalities and other factors that delay oesophageal emptying, such as strictures or inability to stand or sit upright for at least 30 minutes
- Hypocalcaemia (see also section 4.4)
- Known vitamin D hypersensitivity
- Manifest vitamin D intoxication
- Plasma calcium concentrations above 2.6 mmol/l, a calcium phosphate product above  $3.7 \text{ (mmol/l)}^2$  and alkalosis with pH levels above 7.44 in venous blood (milk-alkali syndrome, Burnett's syndrome)
- Hypercalcaemia
- Hypermagnesaemia
- Patients on dialysis
- Patients with a history of renal stones or with sarcoidosis are at greater risk
- Children and adolescents
- Achalasia

Both components of Teboneva, alendronic acid and alfacalcidol, may exert opposite effects to avoid major fluctuations

in serum calcium concentrations. Both substances can influence calcium concentrations in the blood: alendronic acid can reduce them, whilst alfacalcidol can increase them. The treating doctor should take this into account.

#### 4.4 Special warnings and precautions for use

##### Alendronic acid tablets:

Alendronic acid can cause local mucosal irritation in the upper gastrointestinal tract. Because there is a potential for worsening of the underlying disease, alendronic acid should be used with particular caution in the following persons: patients with active problems in the upper gastrointestinal region, such as dysphagia, oesophageal disorders, gastritis, duodenitis, ulcers, or patients with a recent history (within the previous year) of major gastrointestinal disorders, such as peptic ulcer or active gastrointestinal bleeding, or surgery on the upper gastrointestinal tract other than pyloroplasty (see also section 4.3).

Oesophageal reactions (sometimes severe with the need for hospitalisation) such as oesophagitis, oesophageal ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been described in patients receiving alendronic acid. The treating physicians should therefore be alert for any signs or symptoms indicative of possible oesophageal reactions. Patients should furthermore be instructed to discontinue alendronic acid and seek medical assistance if they notice symptoms of oesophageal irritation, e.g. dysphagia, pain on swallowing or retrosternal pain, or new or worsening heartburn.

The risk of severe adverse oesophageal effects seems to be greater in patients who fail to take alendronic acid correctly and/or who continue to take it after developing symptoms suggestive of oesophageal irritation. It is therefore extremely important to provide the patient with full dosing instructions and to ensure that she understands them (see section 4.2). Patients should be informed that failure to follow these instructions may increase the risk of oesophageal problems.

In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronic acid on an individual patient basis.

Whilst no increased risk was observed in extensive clinical studies, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some of which were severe and associated with complications. A causal relationship cannot be excluded.

Osteonecrosis of the jaw, usually 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 oral bisphosphonates in patients with poor dental status.

During treatment, patients should avoid invasive orthodontic procedures as much as possible. For patients who develop osteonecrosis of the jaw during 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 judgement of the treating physician should guide the management plan for each patient, based on an individual benefit/risk assessment.

During bisphosphonate treatment, all patients 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.

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term 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.

Osteodynia, arthralgia and/or myalgia have been reported in patients on bisphosphonate therapy. In rare cases during post-marketing experience, these symptoms were serious and/or associated with restricted mobility (see section 4.8). Time to onset of these symptoms varied from one day to several months after the start of therapy. In most patients, the symptoms regressed upon discontinuation of therapy. Symptoms recurred in a number of patients when therapy was resumed with the same or a different bisphosphonate.

Patients should be instructed that, after forgetting a dose of alendronic acid, they should take one tablet on the morning after realising their omission. They should not take two tablets on the same day, but should continue taking one tablet once weekly, as originally intended, on their selected day.

Alendronic acid is not recommended for patients with impaired renal function where GFR is less than 35 ml/min (see section 4.2).

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

Hypocalcaemia must be corrected before initiating therapy with alendronic acid (see section 4.3). Other disturbances of mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated. In patients with such disorders, serum calcium concentrations and symptoms of hypocalcaemia should be monitored during therapy with alendronic acid.

Due to the positive effects of alendronic acid on increased bone mineral levels, decreases in serum calcium and phosphate concentrations may occur. These are generally minor and asymptomatic. However, there are rare reports of symptomatic and occasionally severe hypocalcaemia, often occurring in patients with predisposing disorders (e.g. hypoparathyroidism, vitamin D deficiency and calcium malabsorption).

Ensuring adequate calcium intake is of particular importance in patients receiving glucocorticoids.

#### Alfacalcidol capsules, soft:

Alfacalcidol can increase the extent of hypercalcaemia and/or hypercalciuria when administered to patients with disorders associated with uncontrolled overproduction of calcitriol (e.g. leukaemia, lymphomas, sarcoidosis). Urinary and serum calcium concentrations should be monitored in such patients. The clinical symptoms of hypercalcaemia are uncharacteristic (e.g. weakness, fatigue, feeling thirsty, gastrointestinal symptoms and itching). Hypercalcaemia can be rapidly corrected by stopping treatment until plasma calcium levels return to normal.

Patients with rare hereditary problems of fructose intolerance should not take alfacalcidol 1 microgram capsules and should therefore not be treated with Teboneva.

As, due to insufficient experience, alendronic acid cannot be recommended for patients with severely impaired renal function (creatinine clearance below 35 ml/min).

Teboneva is not recommended for the treatment of patients on dialysis.

Teboneva contains arachis oil (peanut oil). If you are allergic to peanut or soya, do not use this medicinal product.

Teboneva contains alcohol (less than 100mg per capsule).

## 4.5 Interaction with other medicinal products and other forms of interaction

### Alendronic acid tablets:

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

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

Although specific interaction studies were not performed, in clinical studies alendronate was used concomitantly with a wide range of commonly prescribed medicinal products without evidence of clinical adverse interactions.

### Alfacalcidol capsules, soft:

Vitamin D and its derivatives must not be administered together with alfacalcidol.

As alfacalcidol is a highly potent vitamin D derivative, concomitant intake probably causes an additive effect and thus carries an increased risk of hypercalcaemia.

In patients treated with digitalis preparations, hypercalcaemia can lead to cardiac arrhythmias.

Patients concomitantly taking a digitalis preparation and alfacalcidol 1 microgram capsules must therefore be closely monitored.

Patients taking alfacalcidol 1 microgram capsules and barbiturates or enzyme-inducing anticonvulsants require higher dosages of alfacalcidol in order to achieve the desired effect. Diphenyl hydantoin can also impair the effect of alfacalcidol.

Glucocorticoids can likewise attenuate the effect of alfacalcidol.

As bile salts play an important role in the absorption of alfacalcidol, long-term treatment with bile acid sequestrants (cholestyramine, colestipol), sucralfate and antacids with high aluminium content may be harmful. Alfacalcidol 1 microgram capsules and aluminium-containing antacids should therefore not be taken concomitantly and an interval of 2 hours should be respected.

The effect of alfacalcidol is potentiated by co-administration of oestrogens in peri- and postmenopausal women.

The risk of hypercalcaemia is increased by concomitant administration of calcium-containing products, thiazides diuretics or other medicinal products that increase blood calcium concentrations.

## 4.6 Fertility, pregnancy and lactation

Teboneva is only intended for use in postmenopausal women and therefore it should not be used during pregnancy or in breast-feeding women.

Pregnancy

There are no adequate data from the use of Teboneva in pregnant women. Animal studies with alendronate 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 hypocalcaemia (see section 5.3). Studies in animals have shown hypercalcaemia and reproductive toxicity with high doses of vitamin D (see section 5.3).

Breastfeeding

It is not known whether alendronate is excreted into human breast milk. Alfacalcidol and some of its active metabolites pass into breast milk.

Fertility

Bisphosphonates are incorporated into the bone matrix, from which they 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 on ability to drive and use machines

Alendronic acid and alfacalcidol have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Alendronic acid:

In a one year study in postmenopausal women with osteoporosis, the overall safety profile of alendronic acid 70 mg tablets once weekly (n = 519) was comparable to that of alendronic acid 10 mg once daily (n = 370).

In two 3 year studies of virtually identical design in postmenopausal women (alendronic acid 10 mg: n = 196, placebo: n = 397), the overall safety profiles of alendronic acid 10 mg once daily and placebo were comparable.

Adverse events reported by the investigators to be possibly, probably or definitely medicinal product related are presented below if they occurred in 2 1% of patients treated with alendronic acid 10 mg once daily and at a higher incidence than in patients receiving placebo in the 3 year studies (see Table 1):

|                         | 1-year study                                    |  | 3-year studies                                 |                       |
|-------------------------|---|--|--|-----------------------|
|                         | Alendronic acid 70 mg once weekly (n = 519) [%] | Alendronic acid 10 mg once daily (n = 370) [%] | Alendronic acid 10 mg once daily (n = 196) [%] | Placebo (n = 397) [%] |
| <b>Gastrointestinal</b> |   |  |  |                       |
| Abdominal pain          | 3.7   | 3.0  | 6.6  | 4.8                   |
| Dyspepsia               | 2.7   | 2.2  | 3.6  | 3.5                   |
| Acid reflux             | 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                   |
| Gastric ulcer           | 0.0   | 1.1  | 0.0  | 0.0                   |

|   |     |     |     |     |
|---|-----|-----|-----|-----|
| Oesophageal ulcer                             | 0.0 | 0.0 | 1.5 | 0.0 |
| <b>Musculoskeletal</b>                        |     |     |     |     |
| Musculoskeletal pain (bone, muscle or joints) | 2.9 | 3.2 | 4.1 | 2.5 |
| Muscle cramps                                 | 0.2 | 1.1 | 0.0 | 1.0 |
| <b>Neurological</b>                           |     |     |     |     |
| Headache                                      | 0.4 | 0.3 | 2.6 | 1.5 |

The following undesirable effects have also been reported during clinical studies and/or during post-marketing use:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

**Alendronic acid tablets:**

*Immune system disorders:*  
Rare: hypersensitivity reactions, including urticaria and angioedema.

*Metabolism and nutrition disorders:*  
Rare: symptomatic hypocalcaemia [mostly in patients with predisposing factors (see section 4.4)].

*Nervous system disorders:*  
Common: headache, dizziness  
Uncommon: dysgeusia (frequency in clinical trials was similar in the medicinal product and placebo group).

*Eye disorders:*  
Uncommon: eye inflammation (uveitis, scleritis, episcleritis).

*Ear and labyrinth disorders:*  
Common: vertigo (frequency in clinical trials was similar in the medicinal product and placebo group).

*Gastrointestinal disorders:*  
Common: abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer\*, dysphagia\*, abdominal distension, acid regurgitation.

Uncommon: nausea, vomiting, gastritis, oesophagitis\*, oesophageal erosions\*, melena (frequency in clinical trials was similar in the medicinal product and placebo group).

Rare: oesophageal stricture\*, oropharyngeal ulceration\*, perforation, ulcer and bleeding in the upper gastrointestinal tract (PUBs).  
\* See sections 4.2 and 4.4.

*Skin and subcutaneous tissue disorders:*  
Common: alopecia, pruritus (frequency in clinical trials was similar in the medicinal product and placebo group).  
Uncommon: rash, erythema.

Rare: rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (this adverse reaction was identified through post-marketing surveillance. The frequency of rare was estimated based on relevant clinical trial).

*Musculoskeletal and connective tissue disorders:*

Very common: musculoskeletal pain (bones, muscles and joints) which is sometime severe (frequency in clinical trials was similar in the medicinal product and placebo group – see section 4.4).

Common: joint swelling (frequency in clinical trials was similar in the medicinal product and placebo group).

Rare: osteonecrosis of the jaw (this adverse reaction was identified through post-marketing surveillance. The frequency of rare was estimated based on relevant clinical trials – see section 4.4).

*General disorders and administration site conditions:*

Common: asthenia, peripheral oedema (frequency in clinical trials was similar in the medicinal product and placebo group).

Uncommon: transient symptoms of an acute phase reaction (myalgia, malaise and rarely fever), usually in association with initiation of treatment (frequency in clinical trials was similar in the medicinal product and placebo group).

During post-marketing experience the following reactions have been reported (frequency rare): Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

*Alfacalcidol capsules, soft:*

The following adverse events have reported in patients treated with alfacalcidol capsules

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

Rare: allergic reactions, anaphylactic shock (caused mainly by the peanut oil which is one of the ingredients in the capsules), hypercalcaemia (increased blood calcium concentration). The clinical symptoms of hypercalcaemia are uncharacteristic (e.g. weakness, fatigue, feeling thirsty, gastrointestinal symptoms and itching).

Very rare: heterotopic calcifications (cornea and blood vessels) can occur in patients taking alfacalcidol and have been shown to be reversible.

Previous experience has shown that mild, transient elevations in phosphate concentrations occur only rarely in patients taking alfacalcidol. Such rises can be counteracted by administration of phosphate absorption inhibitors (e.g. calcium preparations).

In patients on therapy with alfacalcidol capsules, blood concentrations of calcium and phosphate must be regularly monitored. Such checks should be performed at weekly to monthly intervals. More frequent measurements may be necessary at the start of treatment.

Both components of Tevanebo, alendronic acid and alfacalcidol, may exert opposite effects to avoid major fluctuations in serum calcium concentrations. Both substances can influence calcium concentrations in the blood: alendronic acid can reduce them, whilst alfacalcidol can increase them. The treating physician should take this into account.

Reporting of suspected adverse reactions

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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: <http://www.hpra.ie/>; E-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).



## 4.9 Overdose

### *Alendronic acid:*

Hypocalcaemia, hypophosphataemia and upper gastrointestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis or ulcers, may result from an oral overdose.

There is no specific experience regarding treatment of an overdose with alendronic acid. Milk or antacids should be taken to bind alendronic acid. Due to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain in a fully upright position.

### *Alfacalcidol:*

No damage was observed in patients having accidentally taken a single overdose (25-30 µg alfacalcidol).

Prolonged overdose with alfacalcidol capsules may induce hypercalcaemia, which may be life threatening in certain circumstances.

The clinical picture of hypercalcaemia syndrome is uncharacteristic: asthenia, fatigue, exhaustion, headache, gastrointestinal symptoms (nausea, vomiting, constipation or diarrhoea, heartburn), dry mouth, pain in the muscles, bones and joints, pruritus or palpitations. Polyuria, polydipsia, nocturia and proteinuria may also occur if the renal concentrating ability is impaired. In addition to a dose reduction or temporary discontinuation of alfacalcidol, the following measures may be taken, depending on the severity of hypercalcaemia: low calcium or calcium free diet, fluid administration, dialysis, high-ceiling diuretics, glucocorticoids and calcitonin.

In the event of an acute overdose, prompt gastric lavage and/or administration of paraffin oil can reduce absorption and accelerate excretion via the faeces.

There is no specific antidote available for alfacalcidol capsules overdose.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Drugs for treatment of bone diseases; drugs affecting bone structure and mineralization - alendronic acid and alfacalcidol, sequential.

ATC code: M05BB06

### *Alendronic acid:*

The active ingredient is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on new bone formation. Preclinical studies have shown that alendronic acid preferentially accumulates at sites of active bone resorption. Osteoclast activity is inhibited, but recruitment or attachment of osteoclasts is not affected. The bone formed during treatment with alendronic acid is of normal quality.

### *Treatment of postmenopausal osteoporosis*

**By definition, osteoporosis is present when bone mineral density (BMD) of the spine or hip region is 2.5 standard deviations below the mean value of a normal young population, or as a previous fragility fracture, irrespective of BMD.**

The therapeutic equivalence of alendronic acid 70 mg once weekly (n = 519) and alendronic acid 10 mg once daily (n = 370) has been shown in an one year multicentre study of post-menopausal women with osteoporosis. The mean increase from baseline in lumbar spine BMD at one year was 5.1% (95% confidence interval [CI]: 4.8-5.4%) in the group administered 70 mg once weekly vs. 5.4% (95% CI: 5.0-5.8%) in the group administered 10 mg once daily.

Mean increases in BMD were 2.3% vs. 2.9% in the femoral neck region and 2.9% vs. 3.1% at the total hip in the 70 mg once-weekly group and the 10 mg once-daily group, respectively. Both treatment groups were also comparable with regard to increases in BMD at other skeletal sites.

The effects of alendronic acid on bone mass and fracture incidence in post-menopausal women were investigated 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, mean increases in BMD at three years with alendronic acid 10 mg once daily compared to placebo were 8.8%, 5.9% and 7.8% in the spine, femoral neck and trochanter, respectively. Total skeletal BMD also increased significantly. The proportion of female patients experiencing one or more vertebral fractures was reduced by 48% with alendronic acid therapy compared to placebo (alendronic acid 3.2% vs. placebo 6.2%). In the two year extension of these studies, BMD at the spine and trochanter region continued to increase, whilst BMD at the femoral neck region and total skeletal BMD were maintained.

FIT consisted of two placebo controlled studies with daily administration of alendronic acid (5 mg once daily over two years and 10 mg once daily over one or two additional years):

- FIT 1: A three year study with 2,027 female patients who had at least one vertebral (compression) fracture at study baseline. In this study, daily administration of alendronic acid reduced the incidence of 1 or more new vertebral fractures by 47% (alendronic acid 7.9% vs. placebo 15.0%). Furthermore, 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 female patients with low bone mass but without a baseline vertebral fracture. In this study, upon analysis of the subgroup of women with osteoporosis (37% of the overall population corresponding to the above definition of osteoporosis), a significant difference was seen in the incidence of hip fractures (alendronic acid 1.0% vs. placebo 2.2%, a reduction of 56%) and in the incidence of 1 or more vertebral fractures (2.9% vs. 5.8%, a reduction of 50%).

#### *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 alendronic acid 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 phosphate to  $\leq 2.0$  mg/dl (0.65 mmol/l) were similar in both treatment groups.

#### *Paediatric patients:*

Alendronic acid has been studied in a small number of patients with osteogenesis imperfecta under the age of 18 years. Results are insufficient to support the use of alendronate sodium in paediatric patients with osteogenesis imperfect.

#### *Alfacalcidol:*

Alfacalcidol (1-alpha-hydroxycholecalciferol) is very rapidly converted in the liver to calcitriol (1,25-dihydroxycholecalciferol). Calcitriol is regarded as the main metabolite of cholecalciferol (vitamin D3) and maintains balance in calcium and phosphate metabolism. The main mechanism of action of alfacalcidol is due to increased concentrations of 1,25-dihydroxycholecalciferol in the circulation, which leads to increased intestinal absorption of calcium and phosphate. This promotes bone mineralisation, reduces parathormone concentrations and inhibits bone resorption.

In persons with impaired 1-alpha-hydroxylation in the kidneys, administration of alfacalcidol allows sufficient formation of calcitriol and hence counteracts vitamin D deficiency.

#### *Combination of alendronic acid and alfacalcidol (Teboneva):*

The combination facilitates treatment of osteoporosis. Both active substances, alendronic acid and alfacalcidol, increase bone mineral levels, but the mechanisms of action are different and synergistic. Alendronic acid inhibits catabolic processes in bone, which is supported by the anabolic effects on bone by alfacalcidol. Alendronic acid reduces the risk of vertebral and non-vertebral fractures, e.g. hip fractures. In some clinical studies, alfacalcidol has been shown to reduce the risk of falls in the elderly. Due to the pharmacological effects of both substances, combined intake reduces the possible risks of hypocalcaemia, hypercalcaemia and hypercalciuria.

## 5.2 Pharmacokinetic properties

### *Alendronic acid:*

#### *Absorption*

In relation to an intravenous reference dose, mean oral bioavailability of alendronic acid was 0.64% in women for doses ranging from 5 to 70 mg when administered after an overnight fasting and 2 hours before a standardised breakfast. Bioavailability decreased accordingly to approximately 0.46% and 0.39% when alendronic acid was taken one hour or half an hour before a standardised breakfast. In osteoporosis studies, alendronic acid was effective when administered at least 30 minutes before the first food or beverage of the day.

Bioavailability was negligible when alendronic acid was taken with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronic acid with coffee or orange juice reduced bioavailability by about 60%.

In healthy subjects, oral administration of prednisone (20 mg three times daily for five days) did not lead to any clinically significant change in the oral bioavailability of alendronic acid (mean increase ranging from 20% to 44%).

#### *Distribution*

Studies in rats have shown that alendronic acid, following intravenous administration of 1 mg/kg, is temporarily distributed in soft tissue, whereupon it is rapidly redistributed to bone or excreted via the urine. The mean steady-state volume of distribution in humans, excluding bone, is at least 28 litres. After therapeutic oral doses, plasma concentrations of active substance are too low for analytical detection (< 5 ng/ml). Protein binding in human plasma is approximately 78%.

#### *Biotransformation*

There is no evidence to suggest that alendronic acid is metabolised in animals or in humans.

#### *Excretion*

Following intravenous administration of a single dose of  $^{14}\text{C}$  alendronic acid, approximately 50% of the radioactivity was excreted into the urine within 72 hours, whilst little or no radioactivity was recovered in the faeces. Following intravenous administration of a single 10 mg dose, renal clearance of alendronic acid was 71 ml/min and systemic clearance did not exceed 200 ml/min. Plasma concentrations fell by more than 95% within six hours after intravenous administration. The terminal half-life in humans is estimated to be more than ten years, taking into account the release of alendronic acid from the skeleton. Alendronic acid is not excreted through the acidic or basic transport systems of the kidneys in rats. The substance is therefore not assumed to affect the excretion of other medicinal products via these transport systems in humans.

#### *Characteristics in patients*

Preclinical studies show that the active substance that is not deposited in bone is rapidly excreted in the urine. In animals, no evidence of any saturation of bone uptake was found after long term administration of cumulative intravenous doses of up to 35 mg/kg. Although there are no clinical data available, renal elimination of alendronic acid, as in animal models, is nevertheless likely to be reduced in patients with impaired renal function. Thus, accumulation of alendronic acid in bone might be expected to be somewhat greater in patients with impaired renal function (see section 4.2).

### *Alfacalcidol:*

Alfacalcidol, the active substance of alfacalcidol 1 microgram capsules, has been tested as a precursor to 1-alpha 25-dihydroxycholecalciferol via radioactive labelling in animal trials and in humans. Rapid hepatic 25-hydroxylation was shown in the presence of renal failure.

## 5.3 Preclinical safety data

Non-clinical studies with the combination of alendronic acid and alfacalcidol have not been conducted.

### *Alendronic acid*

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 alendronic acid 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.

### *Alfacalcidol*

At doses far higher than the human therapeutic range, reproductive toxicity has been observed in animal studies.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablets:

Microcrystalline cellulose

Croscarmellose sodium

Magnesium stearate

Capsules, soft:

Citric acid, anhydrous

Propyl gallate

All-rac- $\alpha$ -tocopherol (vitamin E)

Ethanol anhydrous

Arachis oil (peanut oil) refined

Capsule shell:

Gelatin

Glycerol 85%

Anidrisorb 85/70 (which consists of: sorbitol, sorbitan anhydrides, mannitol, higher polyols and water)

Titanium dioxide (E171)

Printing ink:

Shellac

Iron oxide black/(E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from light and moisture.

## 6.5 Nature and contents of container

Blister (Aluminium/Aluminium) containing 1 tablet (alendronic acid) and 7 capsules, soft (alfacalcidol); pack size of 2, 4 or 12 blisters.

One pack contains:

2 blisters: 2 alendronic acid tablets and 14 alfacalcidol capsules, soft

4 blisters: 4 alendronic acid tablets and 28 alfacalcidol capsules, soft

12 blisters: 12 alendronic acid tablets and 84 alfacalcidol capsules, soft

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

No special requirements

## 7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.  
Computerweg 10  
3542 DR Utrecht  
Netherlands

## 8 MARKETING AUTHORISATION NUMBER

PA0749/166/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9<sup>th</sup> January 2015

## 10 DATE OF REVISION OF THE TEXT