SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alendroninezuur Heumann 70 mg één tablet per week, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect
Each tablet contains 272.07 mg lactose anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to off white, oval, biconvex tablet, approximately 17.30 x 9.20 mm in dimensions, debossed with “AHI” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Alendroninezuur Heumann is indicated in adults for the treatment of postmenopausal osteoporosis. It reduces the risk of vertebral and hip fractures.

4.2 Posology and method of administration

Posology
The recommended dosage is one 70 mg tablet once weekly.

Patients should be instructed that if they miss a dose of Alendroninezuur Heumann, they should take one tablet on the morning after they remember. They should not take two tablets on the same day but should return to taking one 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 ‘Alendroninezuur Heumann’ on an individual patient basis, particularly after 5 or more years of use.

Elderly

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

Renal impairment
No dosage adjustment is necessary for patients with creatinine clearance greater than 35 ml/min. Alendronic acid is not recommended for patients with renal impairment where creatinine clearance is less than 35 ml/min, due to lack of experience.

Paediatric population
The safety and efficacy of Alendroninezuur Heumann in children under 18 years of age has not been established. This medicinal product should not be used in children under 18 years of age. Currently available data for alendronic acid in the paediatric population is described in section 5.1.

Method of administration
Oral use.

To permit adequate absorption of alendronic acid:
Alendroninezuur Heumann 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 alendronic acid (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):

- Alendroninezuur Heumann tablets should only be swallowed upon arising for the day with a full glass of water (not less than 200 ml).

- Patients should only swallow Alendroninezuur Heumann whole. Patients should not chew or crush the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.

- Patients should not lie down for at least 30 minutes after taking Alendroninezuur Heumann and until after the first food of the day.

- Alendroninezuur Heumann should not be taken at bedtime or before arising for the day.

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

Alendronic acid Once Weekly 70 mg has not been investigated in the treatment of glucocorticoid-induced osteoporosis.

4.3 Contraindications

Alendronic acid is contraindicated in:
- Hypersensitivity to the active substance 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.

4.4 Special warnings and precautions for use

Upper gastrointestinal adverse reactions
Alendronic acid 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 alendronic acid is given to patients with active upper gastro-intestinal problems, such as dysphagia, oesophageal disease, gastritis, duodenitis, ulcers, or with a recent history (within the previous 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 ulcers and oesophageal erosions, rarely followed by oesophageal stricture, have been reported in patients receiving alendronic acid. Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronic acid and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain, new or worsening heartburn (see section 4.8).

The risk of severe oesophageal adverse experiences appears to be greater in patients who fail to take alendronic acid properly and/or who continue to take alendronic acid 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 their risk of oesophageal problems.

While no increased risk was observed in extensive clinical trials, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications (see section 4.8).

Osteonecrosis of the jaw
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, angiogenesis inhibitors, 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.

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 judgement of the treating physician should guide the management plan of each patient based on 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.

Osteonecrosis of the external auditory canal
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 such as pain or discharge or chronic ear infections.

Musculoskeletal pain
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 treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.

Atypical fractures of the femur
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.

Renal impairment
Alendronic acid is not recommended for patients with renal impairment where creatinine clearance is less than 35 ml/min, (see section 4.2).

Bone and mineral metabolism
Causes of osteoporosis other than oestrogen deficiency, ageing and glucocorticoid use should be considered.

Hypocalcaemia must be corrected before initiating therapy with alendronic acid (see section 4.3). Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting this medicinal product. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with Alendroninezuur Heumann.

Due to the positive effects of alendronic acid in increasing bone mineral, decreases 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 hypocalcaemia, 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 lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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 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 alendronic acid. 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 alendronic acid 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
There are no or limited amount of data from the use of alendronate in pregnant women.
Studies in animals have shown reproductive toxicity. Alendronate given during pregnancy in rats caused dystocia related to hypocalcemia (see section 5.3).
Alendroninezuur Heumann should not be used during pregnancy.

Breast-feeding
It is unknown whether alendronic acid/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.
Alendroninezuur Heumann should not be used during breast-feeding.

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 foetal risk in humans. However, there is a theoretical risk of foetal 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

Alendroninezuur Heumann has no or negligible direct influence on the ability to drive and use machines. Patients may experience certain adverse reactions (for example blurred vision, dizziness and severe bone muscle or joint pain (see section 4.8)) that may influence the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
In a one-year study in post-menopausal women with osteoporosis the overall safety profiles of Alendronate Once Weekly 70 mg (n=519) and alendronic acid 10 mg/day (n=370) were similar.

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

Adverse experiences 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 alendronic acid 10 mg/day and at a greater incidence than in patients given placebo in the three-year studies:

	One-Year Study		**Three-Year Studies**	
	Alendronic acid Once Weekly 70 mg (n = 519) %	Alendronic acid 10 mg/day (n = 370) %	Alendronic acid 10 mg/day (n = 196) %	Placebo (n = 397) %
Gastrointestinal				
abdominal pain	3,7	3,0	6,6	4,8
Dyspepsie	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 distention	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
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	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

Tabulated list of adverse reactions
The following adverse experiences have also been reported during clinical studies and/or post-marketing use:

Frequencies are defined as: 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 including isolated cases)

System Organ Class	Frequency	Adverse reactions
Immune system disorders	Rare	hypersensitivity reactions including urticaria and angioedema
Metabolism and nutrition disorders	Rare	symptomatic hypocalcaemia, often in association with predisposing conditions§
Nervous system disorders	Common	headache, dizziness†
	Uncommon	dysgeusia†
Eye disorders	Uncommon	eye inflammation (uveitis, scleritis, or episcleritis)
Ear and labyrinth disorders	Common	vertigo†
	Very Rare	osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Gastrointestinal disorders	Common	abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer*, dysphagia*, abdominal distension, acid regurgitation
	Uncommon	nausea, vomiting, gastritis, oesophagitis*, oesophageal erosions*, melena†
	Rare	oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUBs (perforation, ulcers, bleeding) §
Skin and subcutaneous tissue disorders	Common	alopecia†, pruritus†
	Uncommon	rash, erythema
	Rare	rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis‡

Musculoskeletal and connective tissue disorders	Very Common	musculoskeletal (bone, muscle or joint) pain which is sometimes severe†§
	Common	joint swelling†
	Rare	osteonecrosis of the jaw‡§; atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)
General disorders and administration site conditions	Common	asthenia†, peripheral oedema†
	Uncommon	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 medicinal product and placebo group. *See sections 4.2 and 4.4 ‡This adverse reaction was identified through post-marketing surveillance. The frequency of rare was estimated based on relevant clinical trials.		

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 the national reporting system listed in Appendix V*.

4.9 Overdose

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

Management
No specific information is available on the treatment of overdose with alendronic acid. Milk or antacids should be given to bind alendronic acid. Owing to the risk of oesophageal irritation, vomiting 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

Mechanism of action
The active ingredient of Alendroninezuur Heumann, is a bisphosphonate that inhibits osteoclastic bone resorption with no direct effect on bone formation. Preclinical studies have shown preferential localization of alendronic acid 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 alendronic acid is of normal quality.

Clinical efficacy and safety

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 (n=519) and alendronic acid 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% CI: 4.8, 5.4%) in the 70 mg once-weekly group and 5.4% (95% CI: 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 in 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 alendronic acid 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 alendronic acid 10 mg/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 (alendronic acid 3.2% vs placebo 6.2%) in the proportion of patients treated with alendronic acid 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 alendronic acid daily (5 mg daily for 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 alendronic acid daily reduced the incidence of ≥1 new vertebral fracture by 47% (alendronic acid 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 hip fractures (alendronic acid 1.0% vs. placebo 2.2%, a reduction of 56%) and in the incidence of ≥1 vertebral fracture (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 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 phosphate to ≤ 2.0 mg/dl (0.65 mmol/l) were similar in both treatment groups.

Paediatric population

Alendronate sodium 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 imperfecta.

5.2 Pharmacokinetic properties

Absorption

Relative to an intravenous reference dose, the oral mean bioavailability of alendronic acid in women was 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and two hours before a standardised breakfast. Bioavailability was decreased similarly to an estimated 0.46% and 0.39% when alendronic acid was administered 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 whether alendronic acid was administered with, or up to two hours after, a standardised breakfast. Concomitant administration of alendronic acid with coffee or orange juice reduced bioavailability by approximately 60%.

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

Distribution

Studies in rats show that alendronic acid transiently distributes to soft tissues following 1 mg/kg intravenous administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 litres 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 alendronic acid is metabolised in animals or humans.

Elimination

Following a single intravenous dose of [^{14}C] alendronic acid, 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 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 following intravenous administration. The terminal half-life in humans is estimated to exceed ten years, reflecting release of alendronic acid from the skeleton. Alendronic acid 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.

Renal impairment

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 alendronic acid via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronic acid 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline (E460)
Lactose anhydrous
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA-Al-PVC/Al blister packed in cartons containing 4, 12 or 24 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

RVG 125274

9. DATE OF FIRST AUTHORISATION OF THE AUTHORISATION

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