ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, APPLICANT, MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Applicant	Invented name Name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
Sweden	HEXAL A/S Kanalholmen 8-12, 2650 Hvidovre, Denmark		Alendronat HEXAL	10mg	Tablets	Oral use	10 mg per tablet
Belgium		HEXAL A/S Kanalholmen 8-12, 2650 Hvidovre, Denmark	Alendronate Sandoz 10mg tabletten	10mg	Tablets	Oral use	10 mg per tablet
Denmark		HEXAL A/S Kanalholmen 8-12, 2650 Hvidovre, Denmark	Alendonicht	10mg	Tablets	Oral use	10 mg per tablet
Greece		HEXAL A/S Kanalholmen 8-12, 2650 Hvidovre, Denmark	Forosa	10mg	Tablets	Oral use	10 mg per tablet

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ALENDRONATE HEXAL AND ASSOCIATED NAMES (see Annex I)

The active substance in Alendronate HEXAL 10 mg tablets, alendronic acid as sodium alendronate trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption without any direct effect on bone formation.

Osteoporosis is defined as bone mineral density (BMD) of the spine or hip 2.5 standard deviations below the mean value of a normal young population or as a previous fragility fracture, irrespective of bone mineral density.
The applicant was asked to further justify the broad indication “treatment of osteoporosis in men” for Alendronate HEXAL.
The Applicant submitted an extensive review of the literature concerning the treatment of osteoporosis in men.

The studies indicated that alendronate 10 mg daily could increase bone mineral density both at vertebral as well as non vertebral level in men with primary osteoporosis. Two studies from Orwell and Ringe demonstrated that compared respectively with placebo or alfacalcidol, alendronate treatment reduced the incidence of vertebral fractures in men with osteoporosis. An effect on non-vertebral fractures has nonetheless not been demonstrated in this population.

GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the literature provided by the applicant provide evidence that 10 mg daily could increase bone mineral density both at vertebral as well as non vertebral level in men with primary osteoporosis,
- an effect on non-vertebral fractures has nonetheless not been demonstrated in this population.

The CHMP has recommended the following indication, which is in accordance with the guideline on the evaluation of medicinal products in the treatment of primary osteoporosis (CHMP/EWP/552/95 Rev.2)

“Treatment of osteoporosis in men at increased risk of fracture. A reduction in the incidence of vertebral, but not of non-vertebral fractures has been demonstrated.”

In addition, other amendments to the Summary of Product Characteristics, labelling and package leaflet not in relation with the outcome of the referral procedure were included in accordance with the Guideline on Summary of Product Characteristics, excipient guideline and the latest Quality Review of Document templates.

The CHMP has recommended the granting of the Marketing Authorisation and the amendment of the Summary of Product Characteristics, labelling, package leaflet of the Reference Member State accordingly for Alendronate HEXAL and associated names (see Annex I) 10 mg tablets.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alendronate HEXAL and associated names (see Annex I) 10 mg tablets

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg alendronic acid (as sodium alendronate trihydrate).

Excipient: 103.95 mg lactose monohydrate per tablet

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White to off-white, capsule-shaped tablet, embossed "AN 10" on one side and "Arrow logo" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of post-menopausal osteoporosis.
Alendronate reduces the risk of vertebral and hip fractures.
Treatment of osteoporosis in men at increased risk of fracture. A reduction in the incidence of vertebral, but not of non-vertebral fractures has been demonstrated.

Prophylaxis of glucocorticoid-induced osteoporosis.
(see section 5.1).

4.2 Posology and method of administration

For oral use only.
Post-menopausal osteoporosis:
The recommended dosage is 10 mg once daily.

Osteoporosis in men:
The recommended dosage is 10 mg once daily.

Glucocorticoid-induced osteoporosis:
For post-menopausal women who are not receiving oestrogen treatment the recommended dose is one 10 mg tablet daily. For other populations, see summary of product characteristics for preparations that contain 5 mg alendronate.

To obtain satisfactory absorption of alendronate
Alendronate HEXAL tablets must be taken on an empty stomach immediately on rising in the morning, with plain water only, at least 30 minutes before the first food, drink or other medication of the day. Other drinks (including mineral water), food and some medicines are likely to reduce the absorption of alendronate (see section 4.5).

To assist delivery to the stomach and thus reduce the risk of irritation/side effects locally and in the oesophagus (see section 4.4)

- Alendronate HEXAL tablets should only be swallowed on rising for the day with a whole glass of water (not less than 200 ml or 7 fl. oz).
- Alendronate HEXAL tablets should be swallowed whole. The tablets should not be chewed, sucked or allowed to dissolve in the mouth on account of the risk of oropharyngeal ulceration.
- Patients should not lie down until after the first meal of the day, which must be at least 30 minutes after taking the tablet.
- Patients should not lie down within 30 minutes of taking Alendronate HEXAL tablets.
- Alendronate HEXAL tablets should not be taken at bedtime or before arising for the day.

Patients should be given a calcium and vitamin D supplement if the diet is inadequate (see section 4.4).

Use in elderly patients:
In clinical trials there was no age-related difference with regard to efficacy or safety profiles of alendronate. Therefore no adjustment of the dose is necessary for elderly patients.

Use in impaired renal function
No dose adjustment is necessary in patients with a glomerular filtration rate (GFR) greater than 35 ml/min. Alendronate is not recommended for patients with impaired renal function if the GFR is less than 35 ml/min, as there is no experience of this.

Use in impaired hepatic function
No dose adjustment is necessary.

Use in children
Alendronate HEXAL is not recommended for use in children due to a lack of data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Oesophageal abnormalities and other factors that 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 to the upper gastrointestinal mucosa. As there is a risk of worsening of the underlying disease, caution should be observed if alendronate is given to patients with active upper gastrointestinal tract problems, such as dysphagia, oesophageal disease, gastritis, duodenitis or ulcers, or in cases of recent (during the last year) severe gastrointestinal disease such as gastric ulcer, active gastrointestinal bleeding or surgery in the upper gastrointestinal tract other than pyloroplasty (see section 4.3).

Oesophageal side effects (in some cases severe and requiring hospitalisation) such as oesophagitis, oesophageal ulcers or oesophageal erosions, in rare cases followed by oesophageal stricture, have been reported in patients receiving treatment with alendronate. The physician should therefore be alert to any signs or symptoms of possible oesophageal reaction. The patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

The risk of severe oesophageal side effects is thought to be greater in patients who do not take alendronate correctly and/or continue to take alendronate after developing symptoms indicative of oesophageal irritation. It is very important that complete administration instructions are given to, and understood, by the patient (see section 4.2). Patients should be informed that the risk of oesophageal problems may increase if they do not follow these instructions.

Despite no increased risk having been observed in extensive clinical trials, following marketing of the original preparation there have been reports of rare cases of gastric and duodenal ulcers, some of them severe and with complications. A causal relationship cannot be excluded (see section 4.8).

Alendronate is not recommended for patients with impaired renal function if the GFR is less than 35 ml/min (see section 4.2).

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

Hypocalcaemia must be corrected before treatment with alendronate is initiated (see section 4.3). Other disorders of mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated before starting alendronate. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during treatment with alendronate.

On account of the positive effects of alendronate on the increase in bone mineralisation, reductions in serum calcium and serum phosphate may occur. These are usually slight and asymptomatic. However, in rare cases, symptomatic hypocalcaemia has been reported which occasionally has been severe and often occurred in patients with predisposing conditions (e.g. hypoparathyroidism, vitamin D deficiency and in cases of calcium malabsorption).
It is therefore particularly important to ensure that patients taking glucocorticoids have an adequate calcium and vitamin D intake.

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.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

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.

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. In post-marketing experience, these symptoms have rarely been seen 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.
Alendronate HEXAL tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

If taken at the same time, it is likely that foods and drinks (including mineral water), calcium supplements, antacids and some oral medicines will affect the absorption of alendronate. Patients must therefore wait for at least 30 minutes after taking alendronate before taking any other oral medicine (see section 4.2).

No other clinically significant active substance interactions are expected. A number of patients in the clinical trials received oestrogen (intravaginally, transdermally or orally) concomitantly with alendronate. No undesirable effects could be related to the combination treatment.

No specific interaction studies have been carried out, but alendronate was used in clinical trials concomitantly with a number of other commonly prescribed medicines without any evidence of clinically unfavourable interactions.

4.6 Pregnancy and lactation

There are insufficient data regarding the use of alendronate in pregnant women. Animal studies revealed effects on foetal bone formation at high doses. Alendronate given to pregnant rats caused hypocalcaemia-related dystocia (see section 5.3). In view of the indication, alendronate should not be used during pregnancy.

It is not known whether alendronate is excreted into breast milk in humans. In view of the indication, alendronate should not be used by breast-feeding women.

4.7 Effects on ability to drive and use machines

Alendronate has no influence on the ability to drive and use machines.

4.8 Undesirable effects

In two three-year studies of almost identical design, with post-menopausal women (alendronate 10 mg: n=196; placebo: n=397) the overall safety profiles for alendronate 10 mg daily and placebo were similar.

Adverse reactions reported by the investigators as possibly, probably or definitely related to the active substance are presented below if they occurred in ≥ 1 % of any in the treatment groups in the one-year study or in ≥ 1 % of the patients who were treated with alendronate 10 mg per day and with an incidence higher than in patients who were treated with placebo in three-year studies.

	Three-year studies	
	Alendronate10 mg daily (n=196) %	*Placebo (n=397) %*
Gastrointestinal		
Abdominal pain	6.6	4.8
Dyspepsia	3.6	3.5
Acid regurgitation	2.0	4.3
Nausea	3.6	4.0
Abdominal distension	1.0	0.8
Constipation	3.1	1.8
Diarrhoea	3.1	1.8
Dysphagia	1.0	0.0
Flatulence	2.6	0.5

	Three-year studies	
	Alendronate10 mg daily (n=196) %	*Placebo (n=397) %*
Gastritis	0.5	1.3
Gastric ulcer	0.0	0.0
Oesophageal ulcer	1.5	0.0
Musculoskeletal		
Musculoskeletal pain (bone, muscle or joints)	4.1	2.5
Muscle cramps	0.0	1.0
Neurological		
Headache	2.6	1.5

The following undesirable effects have also been reported in clinical trials and/or post marketing:

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, not known (cannot be estimated from the available data)

Nervous system disorders:
Common (≥1/100, <1/10): Headache

Eye disorders:
Rare (≥1/10,000, <1/1000): Uveitis, scleritis, episcleritis

Gastrointestinal disorders:
Common (≥1/100, <1/10): Abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcers*, dysphagia*, abdominal distension, acid regurgitation.
Uncommon (≥1/1000, <1/100): Nausea, vomiting, gastritis, oesophagitis* oesophageal erosions*, melaena.
Rare (≥1/10,000, <1/1000): Oesophageal stricture*, oropharyngeal ulceration*, upper gastrointestinal PUB (perforations, ulcers, bleeding), a causal relationship cannot be ruled out.
Very rare, not known: perforation of the oesophagus was reported in isolated cases

*See section 4.2 and 4.4.

Skin and subcutaneous tissue disorders:
Very rare (≤1/10,000): Isolated cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Musculoskeletal and connective tissue disorders:
Common (≥1/100, <1/10): Musculoskeletal pain (bones, muscles or joints)
Rare (≥1/10,000, <1/1000): Severe musculoskeletal (bone, muscle or joint pain) (see section 4.4)
Unknown frequency: Osteonecrosis

General disorders and administration site conditions:
Uncommon (≥1/1000, <1/100): Rash, pruritus, erythema.
Rare (≥1/10,000, <1/1000): Hypersensitivity reactions including urticaria and angioedema. Transient symptoms as in an acute phase reaction (myalgia, malaise and in rare cases fever) usually in connection with the start of treatment. Skin rash with photosensitivity. Symptomatic hypocalcaemia, generally in connection with predisposing conditions (see. Section 4.4).

During post-marketing experience the following reactions have been reported (frequency unknown):

Nervous system disorders:
dizziness

Ear and labyrinth disorders:
vertigo

General disorders and administration site conditions:
asthenia, peripheral oedema

Musculoskeletal and connective tissue disorders:Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and/or local infection (including osteomyelistis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4). joint swelling

Laboratory values: In clinical trials, asymptomatic, slight and transient decreases in serum calcium and serum phosphate were observed in approx. 18 and 10 % respectively of the patients taking alendronate 10 mg/day versus 12 and 3 % respectively of those taking placebo. However, the incidence of reductions in serum calcium to <2.0 mmol/l and serum phosphate to ≤0.65 mmol/l was comparable in the two groups.

4.9 Overdose

Hypocalcaemia, hypophosphataemia and upper gastrointestinal side effects such as upset stomach, heartburn, oesophagitis, gastritis or ulcer can occur on oral overdosage. There is no specific information available with regard to overdosage with alendronate. Milk or antacids should be given in order to bind alendronate. On account of the risk of oesophageal irritation, vomiting should not be induced and the patient should be kept in an upright position.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of bone diseases, bisphosphonates.
ATC code: M05BA04

The active substance in Alendronate HEXAL tablets, sodium alendronate trihydrate, is a bisphosphonate that inhibits osteoclastic bone resorption without any direct effect on bone formation. Preclinical studies have demonstrated a preference for localisation of alendronate to sites where active resorption takes place. Osteoclastic activity is inhibited, but formation and binding of the osteoclasts is not affected. Bone formed during treatment with alendronate is of normal quality.

Treatment of post-menopausal osteoporosis

Osteoporosis is defined as bone mineral density (BMD) of the spine or hip 2.5 standard deviations below the mean value of a normal young population or as a previous fragility fracture, irrespective of bone mineral density.

The effects of alendronate on BMD and fracture incidence in post-menopausal women were studied in two initial efficacy studies of identical design (n=994), and in the *Fracture Intervention Trial* (FIT: n=6459).

In the initial efficacy studies, the increases in BMD with alendronate 10 mg daily relative to placebo after three years were 8.8 %, 5.9 % and 7.8 % at the spine, femoral neck and trochanter respectively. Total BMD also increased significantly. In the patients treated with alendronate, the proportion of patients who suffered one or more vertebral fractures was reduced by 48 % (alendronate 3.2 % versus placebo 6.2 %). In the two-year extensions of these studies the BMD in the spine and trochanter continued to increase. In addition, BMD at the femoral neck and total body was maintained.

The FIT study included two placebo-controlled trials in which alendronate was given daily (5 mg daily for two years and 10 mg daily for a further one or two years).

- FIT 1: A three-year study with 2027 patients who had 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 % versus placebo 15.0 %). In addition, a statistically significant reduction in the incidence of hip fractures was confirmed (1.1 % versus 2.2 %, a reduction of 51 %).
- FIT 2: A four-year study with 4432 patients who had a low bone mass but had not had any vertebral fracture at the start of the study. In this study, in a subgroup analysis of osteoporotic women (37 % of the total population who fulfilled the definition of osteoporosis given above) a significant difference was seen in the incidence of hip fractures (alendronate 1.0 % versus placebo 2.2 %, a reduction of 56 %) and in the incidence of ≥1 vertebral fracture (2.9 % versus 5.8 %, a reduction of 50 %).

Osteoporosis in men with increased risk of fracture
The efficacy of alendronate 10 mg once daily in men (31-87 years, mean age 63 years, n=241) with osteoporosis was evaluated in a two-year study. After two years of treatment with alendronate 10 mg/day, BMD increased on average by 5.3 % in the spine, by 2.6 % in the femoral neck, by 3.1 % in the trochanter, and by 1.6 % for the skeleton as a whole, relative to placebo ($p<0.001$ for all measurement points). The effect of alendronate on BMD was independent of age, race, gonadal function, baseline BMD or baseline bone turnover. The incidence of new vertebral fractures was evaluated as a safety variable. In a retrospective analysis (assessed by quantitative radiography) one new fracture (0.8 %) was documented among patients treated with alendronate, compared with 6 new fractures (7.1 %) for placebo ($p=0.017$). The reduction in height was less after treatment with alendronate, relative to placebo (-0.6 mm and -2.4 mm respectively, $p=0.02$). No effect on non-vertebral fractures was seen.

Glucocorticoid-induced osteoporosis
Long-term use of steroids is often associated with the development of osteoporosis accompanied by fractures. This occurs in both men and women of all ages. The efficacy of alendronate 10 mg and alendronate 5 mg once daily in men and women treated with steroids (at least 7.5 mg/day of prednisone or equivalent, median dose 10 mg/day) was demonstrated in two one-year studies of practically identical design. These studies involved a total of 560 patients aged 17-83 years. The patients received calcium and vitamin D supplements. Relative to placebo, BMD increased significantly in the spine (2.41 %), femoral neck (2.19 %) and trochanter (1.65 %) in patients who were treated with alendronate 5 mg once daily. The increases in BMD with alendronate 10 mg once daily were the same as for alendronate 5 mg once daily in all patients, with the exception of post-menopausal women who were not being treated with oestrogen. In these women the increases (relative to placebo) with alendronate 10 mg once daily were greater than for alendronate 5 mg once daily in the spine (4.11 % versus 1.56 %) and trochanter (2.84 % versus 1.67 %). The fracture-preventing effect of increasing bone density with alendronate 10 mg or alendronate 5 mg in corticosteroid-induced osteoporosis has not been established.

Alendronate 10 mg and 5 mg were effective irrespective of the dose or duration of steroid use. In addition, alendronate 10 mg and alendronate 5 mg were effective irrespective of age (<65 years as against ≥65 years), gender, baseline BMD, baseline bone turnover and concomitant use of a number of common medicines. In the patients who received alendronate in doses up to 10 mg daily and in whom

biopsy was performed after one year no signs of a disturbance of the bone mineralisation process were seen.

5.2 Pharmacokinetic properties

Absorption
Compared with an intravenous reference dose, the mean oral bioavailability of alendronate in women was 0.64 % for doses ranging from 5 to 70 mg given after an overnight fast and two hours before a standardised breakfast. Bioavailability decreased to an estimated 0.46 % and 0.39 % when alendronate was given an hour or half an hour before a standardised breakfast.
In osteoporosis studies alendronate was effective when it was given at least 30 minutes before the first meal or drink of the day. Bioavailability was negligible irrespective of whether alendronate was given together with or up to two hours after a standardised breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approx. 60 %. In healthy persons, oral prednisolone (20 mg three times daily for five days) did not result in any clinically meaningful change in the oral bioavailability of alendronate (a mean increase ranging from 20 % to 44 %).

Distribution
Studies in rats show that alendronate is initially distributed to soft tissues after intravenous administration of 1 mg/kg, but is then rapidly redistributed to the skeleton or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 litres in humans. Concentrations of active substance 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 intravenous dose of 10 mg, 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 6 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 thought to interfere with the excretion of other active substances by those 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. 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

Conventional studies of general toxicity, genotoxicity and carcinogenicity did not reveal any special risks for humans. Studies in female rats showed that treatment with alendronate during pregnancy was associated with dystocia during parturition, which was related to hypocalcaemia. Studies in which rats were given high doses showed an increased incidence of incomplete foetal bone formation. The relevance for humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

The tablets are supplied in triplex blister (PVC/PE/PVDC/AL) packaging.
14, 28, 56, 98, 112 and 50 x 1 (unit dose).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

<[To be completed nationally]>

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Alendronate HEXAL and associated names (see Annex I) 10 mg tablets

[See Annex I - To be completed nationally]

Alendronic acid

2. STATEMENT OF ACTIVE SUBSTANCE

One tablet contains 10 mg alendronic acid (as sodium alendronate trihydrate).

3. LIST OF EXCIPIENTS

Also contains lactose. Please see package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets
28 tablets
56 tablets
98 tablets
112 tablets
50 x 1 (unit dose) tablet

5. METHOD AND ROUTE OF ADMINISTRATION

For oral use. Please read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

Alendronate HEXAL should be swallowed whole
Alendronate HEXAL must be taken on an empty stomach immediately on rising in the morning, with plain water only, at least 30 minutes before the first food, drink or other medication of the day!
Do not lie down within 30 minutes of taking Alendronat HEXAL

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Please store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

Alendronate HEXAL

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

PVC/PE/PVDC/AL

1. NAME OF THE MEDICINAL PRODUCT

Alendronate HEXAL and associated names (see Annex I) 10 mg tablets
[See Annex I - To be completed nationally]

Alendronic acid

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Alendronate HEXAL and associated names (see Annex I) 10 mg tablets
[See Annex I - To be completed nationally]

Alendronic acid

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT IS ALENDRONATE HEXAL AND WHAT IT IS USED FOR

Alendronate belongs to a group of non-hormonal medicines called bisphosphonates. Alendronate prevents the loss of bone, and helps to rebuild bone. It reduces the risk of spine and hip fractures.

Your doctor has prescribed Alendronate HEXAL to treat your **osteoporosis**. Alendronate HEXAL has been shown to **reduce the risk of spine and hip fractures** in women **and spine fractures** in men.

Osteoporosis is a thinning and weakening of the bones. Early on, osteoporosis usually has no symptoms. If left untreated, however, it can result in broken bones. Although these usually hurt, breaks in the bones of the spine may go unnoticed until they cause height loss. Broken bones can happen during normal, everyday activity, such as lifting, or from minor injury that would not generally break normal bone. Broken bones usually occur at the hip, spine, or wrist and can lead not only to pain but also to considerable problems like stooped posture (‘dowager’s hump’) and loss of mobility.

As well as your treatment with Alendronate HEXAL, your doctor may suggest you make changes to your lifestyle to help your condition, such as:

Stopping smoking
Smoking appears to increase the rate at which you lose bone and, therefore, may increase your risk of broken bones.

Exercise
Like muscles, bones need exercise to stay strong and healthy. Consult your doctor before you begin any exercise programme.

Eating a balanced diet
Your doctor can advise you about your diet or whether you should take any dietary supplements.

2. BEFORE YOU TAKE ALENDRONATE HEXAL

Do not take Alendronate HEXAL
- if you are allergic (**hypersensitive)** to alendronate sodium trihydrate or any of the other ingredients of Alendronate HEXAL
- if you have **certain problems with your gullet** (oesophagus - the tube that connects your mouth with your stomach) such as narrowing or difficulty swallowing
- if you cannot **stand or sit upright for at least 30 minutes**
- if your doctor has told you that you have **low blood calcium**

If you think any of these apply to you, do not take the tablets. Talk to your doctor first and follow the advice given.

Take special care with Alendronate HEXAL
Tell your doctor
- if you suffer from **kidney problems**
- if you have any **swallowing or digestive problems**
- if you have **low blood calcium levels**.

Irritation, inflammation or ulceration of the gullet (oesophagus - the tube that connects your mouth with your stomach) often with symptoms of chest pain, heartburn, or difficulty or pain upon swallowing may occur, especially if patients do not drink a full glass of water and/or if they lie down less than 30 minutes after taking Alendronate HEXAL. These side effects may worsen if patients continue to take Alendronate HEXAL after developing these symptoms.

Talk to your doctor before you take Alendronate HEXAL if you have or have had pain or swelling of your gums and/or jaw, numbness of the jaw, if the jaw feels heavy or if you have lost a tooth. This might be a symptom of osteonecrosis (death of bone tissue). Talk to your doctor if you suffer from cancer or if your teeth are in bad condition as this is a risk factor. If you are being treated by a dentist or if you are going to have dental surgery, tell your dentist that you are taking Alendronate HEXAL.

Alendronate HEXAL should not be given to children and adolescents.

Taking other medicines
It is likely that **calcium supplements**, **antacids**, and **some oral medicines** will interfere with the absorption of Alendronate HEXAL if taken at the same time. Therefore, it is important that you follow the advice given in section 3. “How to take Alendronate HEXAL”.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Alendronate HEXAL with food and drink
It is likely that food and beverages (including mineral water) will make Alendronate HEXAL less effective if taken at the same time. Therefore, it is important that you follow the advice given in section 3. “How to take Alendronate HEXAL”.

Pregnancy and breast-feeding
You should not take Alendronate HEXAL if you are or think you may be pregnant.

You should not take Alendronate HEXAL if you are breast-feeding.

Driving and using machines
Alendronate HEXAL should not affect your ability to drive or operate machines.

Important information about some of the ingredients of Alendronate HEXAL
Alendronate HEXAL contains lactose. If you have been told by your doctor that you have an intolerance to some sugars (for example lactose), contact your doctor before taking this medicine.

3. HOW TO TAKE ALENDRONATE HEXAL

Always take Alendronate HEXAL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Take one Alendronate 10 mg tablet <u>once daily</u>.

Follow these instructions carefully to make sure you will benefit from Alendronate HEXAL.

It is very important to follow instructions 1), 2), 3) and 4) to help the Alendronate HEXAL reach your stomach quickly and help reduce the chance of irritating your gullet (oesophagus - the tube that connects your mouth with your stomach).

1) After getting up for the day and before taking any food, drink, or other medicine, swallow your Alendronate HEXAL **with a full glass of water** only (not mineral water) (not less than 200 ml or 7 fl. oz.).
- Do not take with mineral water (still or sparkling).
- Do not take with coffee or tea.
- Do not take with juice or milk.

2) Do not chew the tablet or allow it to dissolve in your mouth.

3) Do not lie down - **stay fully upright (sitting, standing or walking) - for at least 30 minutes** after swallowing the tablet. Do not lie down until after your first food of the day.

4) Do not take Alendronate HEXAL at bedtime or before getting up for the day.

5) If you develop difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking Alendronate HEXAL and contact your doctor.

6) After swallowing your Alendronate HEXAL, **wait at least 30 minutes before taking your first food, drink, or other medicine of the day, including antacids, calcium supplements and vitamins**. Alendronate HEXAL is effective only if taken when your stomach is empty.

7) It is important that you continue taking Alendronate HEXAL for as long as your doctor prescribes the medicine. Alendronate HEXAL can treat your osteoporosis only if you continue to take the tablets.

If you take more Alendronate HEXAL than you should
If you take too many tablets by mistake, drink a full glass of milk and contact your doctor immediately. Do not make yourself vomit, and do not lie down.

If you forget to take Alendronate HEXAL
If you miss a dose, just take one tablet on the morning after you remember. Do not take two tablets on the same day. Return to taking one tablet daily.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Alendronate HEXAL can have side effects, although not everybody gets them.

The following terms are used to describe how often side effects have been reported.

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, not known (cannot be estimated from the available data)

Common:
headache
abdominal pain
uncomfortable feeling in the stomach or belching after eating
constipation
full or bloated feeling in the stomach
diarrhoea
flatulence
heartburn
difficulty swallowing
pain upon swallowing
ulceration of the gullet (oesophagus - the tube that connects your mouth with your stomach) which can cause chest pain, heartburn or difficulty or pain upon swallowing
bone, muscle and/or joint pain

Uncommon
Nausea
Vomiting
irritation or inflammation of the gullet (oesophagus - the tube that connects your mouth with your stomach) or stomach
black or tarlike stools
rash
itching
redness of the skin

Rare:
blurred vision, pain or redness in the eye
narrowing of the gullet (oesophagus - the tube that connects your mouth with your stomach)
mouth ulcers when the tablets have been chewed or sucked
stomach or peptic ulcers (sometimes severe or with bleeding) but it is not sure whether these were caused by Alendronate HEXAL.
Severe bone, muscle and/or joint pain
rash made worse by sunlight, transient flu-like symptoms, such as aching muscles, generally feeling unwell and sometimes with fever usually at the start of treatment
hypersensitivity reactions including nettle rash and angio-oedema
symptoms of low blood calcium levels including muscle cramps or spasms and/or tingling sensation in the fingers or around the mouth

Very rare:
severe skin reactions
perforation of the gullet (oesophagus - the tube that connects your mouth with your stomach) was reported in isolated cases

During post-marketing experience the following side effects have been reported (frequency unknown):

dizziness
swelling in the hands or legs
lack or loss of strength
osteonecrosis (death of bone tissue)

joint swelling

It will help if you make a note of what you experienced, when it started and how long it lasted.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ALENDRONATE HEXAL

Keep out of the reach and sight of children.

Do not take the tablets after the expiry date stated on the blister and the carton. The expiry date refers to the last day of that month.

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6. FURTHER INFORMATION

What Alendronate HEXAL contains
The active substance is alendronate sodium trihydrate. Each tablet contains 10 mg alendronic acid as alendronate sodium trihydrate.

The other ingredients are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate.

What Alendronate HEXAL looks like and contents of the pack
Alendronate HEXAL are available as white to off-white, capsule-shaped tablet, embossed "AN 10" on one side and "Arrow logo" on the other.

The tablets are supplied in triplex blister (PVC/PE/PVDC/AL) packs containing 14, 28, 56, 98, 112 and 50 x 1 (unit dose).
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
<[See Annex I - To be completed nationally]>

This medicinal product is authorised in the Member States of the EEA under the following names:>

Sweden - Alendronat HEXAL
Germany - Alendron-HEXAL
Poland - AlendroHEXAL 10
Belgium - Alendronate Sandoz
Denmark - Alendonicht
Greece - Forosa
This leaflet was last approved in {MM/YYYY}.
<[To be completed nationally]>