PROPOSED CLEAN COPY OF PACKAGE INSERT FOR

OSTEOBON-70

SCHEDULING STATUS:

S3

PROPRIETARY NAME (AND DOSAGE FORM):

OSTEOBON-70 (Tablets)

COMPOSITION:

Each **OSTEOBON-70** tablet contains sodium alendronate (alendronate sodium trihydrate) equivalent to 70 mg of alendronic acid.

Inactive ingredients include mannitol, microcrystalline cellulose, sodium starch glycollate, maize starch, and magnesium stearate.

PHARMACOLOGICAL CLASSIFICATION:

A.3.2. Connective tissue medicines, non-hormonal preparations.

PHARMACOLOGICAL ACTION:

Bisphosphonates are synthetic analogues of pyrophosphate that bind to the hydroxyapatite found in bone. Alendronate sodium is an aminobisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption.

Alendronate localises preferentially at sites of bone resorption, specifically under osteoclasts, and inhibits osteoclastic bone resorption with no direct effect on bone formation. Since bone formation and bone resorption are coupled, bone formation is also reduced, but less so than resorption, leading to progressive gains in bone mass. During exposure to alendronate, normal bone is formed that incorporates alendronate into its matrix where it is pharmacologically inactive.

Pharmacokinetics:

Absorption:

The mean oral bioavailability of alendronate in women is 0,57 % for the 70 mg tablet when administered after an overnight fast and two hours before a standardised breakfast.

Bioavailability is decreased by 40 % when alendronate is given either 30 minutes or one hour before breakfast, when compared to taking the tablets two hours before eating.

Bioavailability is negligible whether alendronate is administered with or up to two hours after or before a standardised breakfast.

When alendronate is taken with coffee or citrus juice, bioavailability is reduced by 60 %.

Distribution:

Alendronate is transiently distributed to soft tissue and then rapidly redistributed to bone or excreted in the urine. The volume of distribution is at least 28 ℓ in humans.

Protein binding:

Approximately 78 % in human plasma.

Elimination:

Following a single intravenous dose of 10 mg alendronate, the renal clearance was 71 mℓ per minute. The systemic clearance was approximately 200 mℓ/min. After 6 hours the plasma concentrations fell by more than 95 %. The terminal half-life in humans is estimated to exceed 10 years, reflecting release of alendronate from the skeleton.

There is no evidence that alendronate is metabolised in humans.

INDICATIONS:

OSTEOBON-70 is indicated in women for the treatment of postmenopausal osteoporosis to reduce the risk of fractures, including those of the hip and spine (vertebral compression fractures).

OSTEOBON-70 is also indicated for the treatment of primary hypogonadal osteoporosis in men and to reduce the risk of vertebral fractures.

CONTRA-INDICATIONS:

- Hypersensitivity to alendronate or any other components of the formulation.
- Severe renal function impairment when creatinine clearance is less than 35 mℓ/minute.
- The presence of gastrointestinal problems, such as duodenitis, dysphagia, gastritis, ulcers or symptomatic oesophageal diseases.
- Abnormalities of the oesophagus which delay oesophageal emptying, such as stricture or achalasia.
- The inability to stand or sit upright for 30 minutes after taking the medicine.
- Hypocalcaemia (see **"Special Precautions"**).
- Paediatric age group: safety and efficacy have not been established.

As alendronate may exacerbate hypocalcaemia or vitamin D deficiency, these conditions should be corrected before **OSTEOBON-70** is administered.

WARNINGS:

Localised osteonecrosis of the jaw (ONJ), generally associated with tooth extraction and/or local irritation with delayed healing, has been reported with oral bisphosphonates, such as **OSTEOBON-70** (see **"Side-Effects"**). Most reported cases of bisphosphonate-associated ONJ have been in cancer patients treated with intravenous bisphosphonates. Known risk factors for ONJ include a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids), poor oral hygiene, and co-

morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection). Patients who develop ONJ should receive appropriate care by an oral surgeon and discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment. Dental surgery may exacerbate the condition.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates, including **OSTEOBON-70**, in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible.

For patients requiring invasive dental surgery (e.g. tooth extraction, dental implants), clinical judgement of the treating doctor and/or oral surgeon should guide the management plan, including bisphosphonate treatment, of each patient based on individual benefit/risk assessment.
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.

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in long-term (usually longer than three years) bisphosphonate-treated patients. Some were stress fractures (some of which were reported as

insufficiency fractures) occurring in the absence of apparent trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. Approximately one third of these fractures were bilateral; therefore the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture.

INTERACTIONS:

Other oral medications, such as calcium supplements and antacids, will interfere with the absorption of **OSTEOBON-70**. Patients are advised to wait at least 30 minutes after **OSTEOBON-70** before taking any other oral medication.

No adverse experiences attributable to the concomitant use of **OSTEOBON-70** and oestrogen (intravaginal, transdermal, or oral) in postmenopausal women have been identified.

PREGNANCY AND LACTATION:

The safety of **OSTEOBON-70** has not been established in pregnancy or lactation.

DOSAGE AND DIRECTIONS FOR USE:

It is important to take **OSTEOBON-70** only as directed.

The recommended dosage is one **OSTEOBON-70** tablet (70 mg alendronic acid) once weekly, taken by mouth with a glass of plain water, at least 30 minutes before any food, beverages or other medication is taken.

It is important to take **OSTEOBON-70** with plain water only, as other beverages, including mineral water, are likely to reduce the absorption of alendronic acid.

All patients should take calcium and vitamin D supplements if their diet is inadequate. These should be taken at least 30 minutes after taking **OSTEOBON-70**.

Patients should remain in an upright position for 30 minutes after taking **OSTEOBON-70** tablets.

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, **OSTEOBON-70** should only be swallowed upon arising for the day with a full glass of water and patients should not lie down for at least 30 minutes and until after their first food of the day. **OSTEOBON-70** should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of oesophageal adverse experiences (see **"Special Precautions"**).

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mℓ/min) (see **"CONTRA-INDICATIONS"**).

Missed dose:

Do not take the missed dose later in the day. Resume the usual schedule the next morning. Do not take two tablets on the same day, return to taking one tablet once a week, as originally scheduled on your chosen day.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

The following adverse reactions have been reported with **OSTEOBON-70** once weekly:

Nervous system disorders:

Frequent: Headache.

Eye disorders:

Less frequent: Uveitis.

Gastrointestinal disorders:

Frequent: Abdominal pain, dyspepsia, oesophageal ulcer*, dysphagia*, abdominal distension, oesophagitis*, oesophageal erosions*, nausea, vomiting,

	constipation, diarrhoea, flatulence, acid regurgitation and melaena.
Less frequent:	Oesophageal stricture*, oropharyngeal ulceration*, gastritis, gastric and duodenal ulcers, some severe and with complications, although a causal relationship has not been established. (*See **"DOSAGE AND DIRECTIONS FOR USE"** and **"Special Precautions"**).

Skin and subcutaneous tissue disorders:

Less frequent:	Rash (occasionally with photosensitivity) and erythema.

Musculoskeletal, connective tissue and bone disorders:

Frequent:	Musculoskeletal (bone, muscle or joint) pain.
Less frequent:	Osteonecrosis of the jaw (see **"WARNINGS"**).

Of the above adverse experiences, abdominal pain was reported most commonly and the incidences of the other adverse experiences did not exceed 4,1 %.

Laboratory test findings:

Asymptomatic, mild and transient decreases in serum calcium and phosphate have been observed.

Post-marketing experience:

The following adverse experiences have been reported during post-marketing use of **OSTEOBON-70**:

Immune system disorders:

Less frequent: Hypersensitivity reactions, including urticaria and angioedema.

Metabolism and nutrition disorders:

Less frequent: Symptomatic hypocalcaemia, generally in association with predisposing factors (see **"Special Precautions"**).

Nervous system disorders:

Less frequent: Dizziness, vertigo.

Frequency unknown: Dysgeusia.

Eye disorders:

Less frequent: Uveitis, scleritis, episcleritis.

Gastrointestinal disorders:

Less frequent: Vomiting, oesophagitis*, oesophageal erosions*, oesophageal stricture*, and oesophageal perforations.

(* See **"DOSAGE AND DIRECTIONS FOR USE"** and **"Special Precautions"**.)

Skin and subcutaneous tissue disorders:

Less frequent: Severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, alopecia, rash with photosensitivity, and pruritus.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Severe and/or incapacitating bone, joint and/or muscle pain (see **"Special Precautions"**), joint swelling. Localised osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection, with delayed healing (see **"WARNINGS"**).

Frequency unknown: Stress fractures of the proximal femoral shaft (see **"WARNINGS"**).

General disorders:

Less frequently: Transient symptoms as in an acute phase response (myalgia, malaise, asthenia and fever). Peripheral oedema.

Special Precautions:

Hypocalcaemia and vitamin D deficiency should be corrected before starting **OSTEOBON-70** therapy, as alendronic acid may exacerbate these conditions. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with **OSTEOBON-70**.

The risk benefit should be considered in patients suffering from upper gastrointestinal diseases, such as dysphagia, duodenitis, gastritis, ulcers or symptomatic oesophageal conditions, because of possible irritant effects of **OSTEOBON-70** on the upper gastrointestinal mucosa and a potential for worsening of the underlying disease.

Oesophageal adverse experiences, such as oesophagitis, oesophageal ulcers and oesophageal erosions, infrequently followed by oesophageal stricture, have been reported in patients receiving treatment with alendronate. In some cases these have been severe and required hospitalisation. Doctors should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue **OSTEOBON-70** and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe oesophageal adverse experiences appears to be greater in patients who lie down after taking **OSTEOBON-70** and/or who fail to swallow it with a full glass of water, and/or who continue to take **OSTEOBON-70** after developing symptoms suggestive of oesophageal irritation. Therefore, it is

very important that the full dosing instructions are provided to, and understood by, the patient (see **"DOSAGE AND DIRECTIONS FOR USE"**).

To facilitate delivery to the stomach and thus reduce the potential for oesophageal irritation, patients should be instructed to swallow **OSTEOBON-70** with a full glass of water and not to lie down for at least 30 minutes and until after their first food of the day. Patients should not chew or suck on the tablet because of a potential for oropharyngeal ulceration. Patients should be specifically instructed not to take **OSTEOBON-70** at bedtime or before arising for the day. Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems. Patients should be instructed that if they develop symptoms of oesophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or new or worsening heartburn) they should stop taking **OSTEOBON-70** and consult their doctor.

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

Due to the positive effects of **OSTEOBON-70** to increase bone mineralisation, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients receiving glucocorticoids, in whom calcium absorption may be decreased.
Ensuring adequate calcium and vitamin D intake is especially important in patients receiving glucocorticoids.

Bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates, such as **OSTEOBON-70**. 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 medicine or another bisphosphonate.

Use in the elderly:

There is no age-related difference in the efficacy or safety profiles of alendronate.

Effects on ability to drive and use machines:

There are no data to suggest that **OSTEOBON-70** affects the ability to drive or use machines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Hypocalcaemia, hypophosphataemia and upper gastrointestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage. The administration of milk and antacids may be of benefit.

Because of the risk of oesophageal irritation, vomiting should not be induced. Keep the patient in an upright position.

IDENTIFICATION:

White, capsule-shaped, biconvex tablets, plain on one side and '3173' debossed on the other side.

PRESENTATION:

OSTEOBON-70 tablets are supplied in a PVC/PVDC coated clear transparent film and aluminium foil blister strip of 4 tablets.

STORAGE INSTRUCTIONS:

Store in a dry place at or below 25 °C.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

A39/3.2/0396

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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