Safety concern	Routine risk minimisation measures	Additional risk minimisation measures

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Osteoporosis means porous bones. It is a "silent" disease that is often undiagnosed until a fracture/s (broken bone/s) occurs.

Sufficient levels of sex hormones, calcium, vitamin D, calories, proteins and weight bearing/strengthening exercise are required to keep bone healthy. With age, more bone is lost than is replaced, but osteoporosis sufferers lose more bone than is normal. This causes bones to become fragile and prone to fractures e.g. through minor bumps or falls. Osteoporosis can affect the whole skeleton, but common areas to break are the wrist, spine and hip. The disease affects all age groups and both sexes.

Usually the first sign of Osteoporosis is a fragility (low trauma) fracture e.g. a broken bone due to a trip and fall from a standing position or less.

In 2010 twenty-two million women and 5.5 million men in the EU were estimated to have osteoporosis; and 3.5 million new fragility fractures were sustained. Approximately 5,500,000 osteoporotic men and 22,100,000 osteoporotic women resided in the EU27 in 2010, i.e. there were four times as many women with osteoporosis as there were men. Two thirds of all incident fractures occurred in women. In 2010, the number of deaths causally related to fractures was estimated at 43,000. Approximately 50 % of fracture related deaths in women were due to hip fractures. The economic burden of incident and prior fragility fractures was estimated at € 37 billion in 2010.[1]

1. E. Hernlund & A. Svedbom & M. Ivergård & J. Compston & C. Cooper & J. Stenmark & E. V. McCloskey & B. Jönsson & J. A. Kanis. Osteoporosis in the European Union: Medical Management, Epidemiology and Economic Burden. Arch Osteoporos (2013) 8:136

VI.2.2 Summary of treatment benefits

The active substance in Alendronic Acid 70mg Oral Solution Once Weekly, alendronic acid, is a bisphosphonate that inhibits bone resorption without affecting bone formation. Alendronic acid localizes in the bone at sites of active resorption. The bone formed during treatment with alendronate is of normal quality.
The efficacy of alendronic acid 70 mg once-weekly was shown to be the same as alendronic acid 10 mg daily n a one-year multicentre study of post-menopausal women with osteoporosis. This study showed that increases in bone mineral density (BMD) in both groups were equivalent in areas such as; lumbar spine, femoral neck, and hip..
The effects of alendronic acid on bone mass and fracture incidence in post-menopausal women were examined in the Fracture Intervention Trial (FIT: n=6,459).

FIT :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, 2,027 patients with ≥ one baseline vertebral fracture. Alendronic acid reduced the incidence of 1 new vertebral fracture by 47%. In addition, a 51%reduction was found in the incidence of hip fractures (.

• FIT 2: A four-year study, 4,432 patients with low bone mass without a baseline vertebral fracture. A significant difference was observed, in the analysis of the subgroup of osteoporotic women:
A reduction of 56%, in the incidence of hip fractures: (in the alendronic acid versus the placebo group)).
A reduction of 50% in the incidence of 1 new vertebral fracture (

VI.2.3 Unknowns relating to treatment benefits

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

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.

Alendronic acid has not been investigated in the treatment of glucocorticoid-induced osteoporosis.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hypersensitivity	Some patients may have a known allergy to Alendronic Acid or to any of the excipients of this product.	This product is contraindicated in patients with known allergy to Alendronic Acid or to any of the excipients of this product. This is a prescription only medication.
Oesophageal Reactions	Alendronic Acid 70mg oral solution 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 70mg oral solution is given to patients with active upper gastro-intestinal problems. This is a prescription only medication.

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.	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, periodontal disease). 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. This is a prescription only medication.
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 including chronic ear infections. Patients are advised to talk to their doctor if they have ear pain, discharge from the ear, and/or an ear infection.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Use in patients with renal impairment (GFR less that 35ml/min),	No dosage adjustment is necessary in patients with a glomerular filtration rate (GFR) greater than 35 ml/min. Alendronic acid is not recommended for patients with impaired renal function where GFR is less than 35 ml/min, due to lack of experience. 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.
Risk of atypical femur fracture with long term use	Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. 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. This is a

Risk	What is known (Including reason why it is considered a potential risk)
	prescription only medication. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of Alendronic acid once weekly 70mg oral solution on an individual patient basis, particularly after 5 or more years of use.
Alcohol content (0.15% volume ethanol may potentially present a trigger effect to alcoholics and in very rare cases may be a risk to those with liver disease or epilepsy	This medicinal product contains 0.15 % volume ethanol (alcohol), i.e. up to 115 mg per dose, equivalent to 3 ml beer or 1.3 ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in high-risk groups such as patients with liver disease, or epilepsy
Patients with untreated hypocalcaemia other untreated disorders affecting mineral metabolism may be adversely effected	Hypocalcaemia must be corrected before initiating therapy with alendronic acid. Other disorders affecting mineral metabolism (such as vitamin D deficiency and hypoparathyroidism) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy with Bonasol Once Weekly. Due to the positive effects of alendronic acid in increasing bone mineral, decreases in serum calcium and phosphate may occur. 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.
Gastrointestinal irritation due to concomitant NSAID use	Since NSAID use is associated with gastrointestinal irritation, caution should be used during concomitant use with alendronate.
Oesophageal irritation following overdo	Hypocalcaemia, hypophosphataemia and upper gastro-intestinal adverse events, such as upset stomach, heartburn, oesophagitis, gastritis, or ulcer, may result from oral overdosage. No specific information is available on the treatment of overdosage with 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

Important Missing information

Use in children and Adolescents	Alendronic acid has been studied in a small number of patients with *osteogenesis imperfecta* under 18 years of age. Results are insufficient to support its use in children.
Pregnancy and lactation	Alendronic should not be used during pregnancy. There are no adequate data from the use of alendronate in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, or postnatal development. Alendronic given during pregnancy in rats caused dystocia

	related to hypocalcemia (see section 5.3). *Use during lactation* It is not known whether alendronate is excreted into human breast milk. Given the indication, alendronic should not be used by breast-feeding women. 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

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Alendronic Acid 70mg oral solution can be found on the following websites: Ireland www.hpra.ie page (RMS), and for the UK www.mhra.gov.uk/spc-pil.

This medicine has no additional risk minimisation measures

VI.2.6 Planned post authorisation development plan (if applicable)

N/A

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
1	At time of authorisation	Identified Risks Potential Risks Missing information	N/A
2		Additional Identified Risks Potential Risks Missing information All included. Format of RMP updated in Line with new legislations and guidelines. Atypical stress fractures added as an identified risk as per Art 31-EMA/H/A-31/1279	N/A
3	Following changeover of PV Provider from Athlone Laboratories to Acorn	Additional Identified Risks Potential Risks Missing information	

Version	Date	Safety Concerns	Comment
	Regulatory Consultancy Services – RMP Revised September 2016 IE/H/0213/001/IA/018 submitted March 2016	All included. Osteonecrosis of the external auditory canal added as identified risk as per Art 31 EMA/PRAC/590240/2015 Submitted as IE/H/0213/001/IA/018	On request from the Dutch MAH, Xeolas were asked to delay submitting the PRAC safety variation IE/H/0213/001/IA/018 until a name change variation and approval of final texts had been completed. This was an error and rectified when Acorn Regulatory commenced as PV Provider for Xeolas and was progressed as quickly as possible.