VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

In most western countries the risk of osteoporosis is about twice as high in women than men, with approximately 40% of women over 60 years of age being affected. The higher incidence of osteoporosis in women reflects, in part, their tendency to live longer than men as well as the occurrence of a period of accelerated bone loss around the time of, and for some years following menopause. Indeed, because of women's higher risk and longer lifespan, there are 3-4 times more hip fracture cases in women than in men.

This said, osteoporosis occurs much more often in some parts of the world than in others, particularly affecting white-skinned people from North America, Northern Europe and elsewhere. The risks for osteoporotic fractures are substantially lower in many parts of Asia, Africa and South America, but the gap is closing with improvements in life expectancy and increasing rates of fracture. Between 1990 and 2025, the estimated size of the population aged over 50 years will increase 130-150% in Europe and about 200% or more in all other regions, with the most marked increase in Asia. These sorts of changes suggest that the number of hip fractures annually will rise from around 1.5 million worldwide in 1990 to between 4 and 6 million in the year 2025.[1]

VI.2.2 Summary of treatment benefits

Alendronate sodium is used to prevent bone diseases such as osteoporosis in men and post-menopausal women, and to prevent post-menopausal osteoporosis and glucocorticoid induced osteoporosis. The clinical efficacy of all these indications have been performed and evaluated in studies which have been conducted for Fosamax by Merck Sharp & Dohme Limited and not by Mylan.

VI.2.3 Unknowns relating to treatment benefits

Little data are available on the use of alendronate sodium in patients below 18 years of age, in patients with severe renal insufficiency and in pregnancy and lactation.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Osteonecrosis of jaw	Osteonecrosis of jaw 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, furthermore osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.	A number of risk factors should be considered when evaluation an individual's risk of developing osteonecrosis of jaw such as potency of the bisphosphonate, route of administration and cumulative dose; whether the patient is a smoker, has cancer and treatments associated with cancer; history of dental disease, poor oral hygiene. Furthermore invasive dental procedures should be avoided. Each patient is instructed to maintain good oral hygiene and receive routine dental check-ups.
Oesophageal adverse experiences	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 alendronate.	The risk of severe oesophageal adverse experiences appears to be greater in patients who fail to take alendronate properly and/or who continue to take alendronate after developing symptoms suggestive of oesophageal irritation. It is very important that the full

Risk	What is known	Preventability
	Physicians should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue alendronate and seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing or retrosternal pain, new or worsening heartburn.	dosing instructions are provided to, and understood by the patient. Patients should be informed that failure to follow these instructions may increase their risk of oesophageal problems

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Atypical femur fracture	Atypical fractures of the thigh bone (femur) 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 upper part of the thigh bone to just above the lower part of the thigh bone. 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 opposite side 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

Risk	What is known (Including reason why it is considered a potential risk)
	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.

Missing information

Risk	What is known
Use in patients below 18 years of age	Alendronate sodium is not recommended for use in children under the age of 18 years due to insufficient data on safety and efficacy in conditions associated with paediatric osteoporosis.
Use in patients with severe renal insufficiency [GFR less than 35 Ml/min]	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 IV 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.
Use in pregnancy and lactation	<u>Pregnancy</u> 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). 'Fosamax' should not be used during pregnancy.

Risk	What is known
	Breast-feeding It is unknown whether alendronate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Alendronate should not be used during breast-feeding

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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. The measures in these documents are known as routine risk minimisation measures. Alendronate sodium does not have any additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

This core RMP is prepared to update the safety concerns for alendronate RMP in line with the safety concerns for innovator product, in line with Guidance on format of the risk management plan (RMP) in the EU for Generics published on 23-Jul-2013 and includes all the Company licenses for alendronate for which Mylan has approved RMPs.

Version 2.0 of the RMP has been amended to version 3.0 as per the RMP preliminary variation assessment report, dated 26-Aug-2016.