1. The National Osteoporosis Foundation of South Africa (NOFSA) was established in 1993 to heighten awareness and increase knowledge on osteoporosis, to promote research in the field, and above all to improve the care of patients suffering from this common, serious disease. The Foundation has always aspired to ensure access, for all those suffering from osteoporosis, to modern diagnostic facilities and effective, safe medication to treat this disease.

2. A variety of drugs, including antiresorptive, anabolic and dual-action agents, are currently available to treat osteoporosis and prevent fractures. Bisphosphonates, which include alendronate and risedronate currently registered in South Africa for the treatment of osteoporosis, are potent antiresorptive drugs which have been shown to be safe and effective in large multicentre, randomised controlled clinical studies.\(^1-4\) Recently, generic alendronate preparations have been introduced to the market.

3. As a group, bisphosphonates are extremely poorly absorbed from the gastrointestinal tract (less than 1%), are bone-selective, and lack systemic metabolism.\(^5\) The absorption of bisphosphonates is nearly totally inhibited by food and beverages other than clear tap water. Bisphosphonates should therefore be taken in the fasting state, with water, at least 30 minutes before food intake.

4. Bisphosphonates have the potential for oesophageal irritation and injury.\(^6-9\) Although rigidly controlled, randomised trials have generally failed to document a high incidence of gastrointestinal side-effects,\(^1-4\) nausea, vomiting, epigastric pain and occasionally severe erosive oesophagitis are not uncommonly encountered in clinical practice. Oesophageal irritation is attributed to prolonged contact of bisphosphonate tablet particles with the oesophageal mucosa, and is exacerbated by underlying gastro-oesophageal reflux disease or hiatus hernia — disorders that occur more commonly in the elderly.

5. Given the rather unique pharmacokinetic properties of the bisphosphonates, it is to be expected that different bisphosphonate formulations/preparations, and the clinical circumstances under which these drugs are used, may be critical in terms of efficacy and safety. This does indeed appear to be the case, for both original and generic bisphosphonate products.

Randomised controlled trials (RCTs) comparing different doses of the original bisphosphonate products have documented significant differences in their ability to increase bone mineral density (BMD) or suppress biomarkers of bone turnover.\(^1,3,10,11\) Significant differences in BMD changes have also been observed in patients taking a particular bisphosphonate, under different circumstances — for example, taking risedronate between meals compared with fasting,\(^12\) or taking ibandronate followed by a 60-minute, compared with a 30-minute, fast.\(^13\)

Side-effects of bisphosphonates, including gastrointestinal disturbances, mineralisation defects, renal impairment, hypocalcaemia, acute-phase reactions and skeletal abnormalities including oversuppression of bone turnover, poor fracture healing and avascular necrosis of the jaw, are likewise profoundly influenced by the particular compound, its dose, route and rate of administration, and the clinical setting in which it is used.\(^1-9, 13-18\)

6. Generic alendronate preparations, largely originating from Latin America and Asia-Pacific countries, have recently been introduced to the market. No data exist to support (or refute) long-term safety or clinical efficacy (fracture risk, BMD, biomarkers of bone turnover) of these agents, since this is not required for registration. Epstein and colleagues\(^19\) have, however, recently compared the disintegration and dissolution profiles of 13 generic alendronate preparations from Latin-America with those of the originator product. Nine generic copies disintegrated 2 - 10-fold faster, and 3 copies disintegrated 5-fold slower, than the originator. The remaining copy exhibited large inter- and intra-lot variability. The authors suggested that slower disintegration may reduce efficacy (the incompletely disintegrated tablet comes into contact with food or liquids, which decrease absorption) and faster
disintegration could increase the risk of oesophagitis (prolonged contact of the oesophageal mucosa with the drug). In a more recent article, Epstein et al.\(^1\) compared the oesophageal irritation profile of the original and generic alendronate preparations. Employing various animal models, a quantitatively greater and qualitatively different inflammatory response compared with the generic agents could be documented. The authors concluded that current bioavailability studies may not be adequate for meaningful assessment of the safety and efficacy of bisphosphonate preparations.

We are unclear as to the clinical significance of these dissolution studies and whether results of animal models of oesophageal irritation can confidently be extrapolated to humans. The results of these studies do, however, suggest that differences may exist between the originator and generic drugs with regard to pharmacokinetics, clinical efficacy and safety.

Bioequivalence studies generally involve clinically irrelevant populations (i.e. young volunteers), free of osteoporosis or other disease, after limited exposure to the drug. The older patient for whom a bisphosphonate is intended would often have other conditions that may affect the safety profile of these drugs (e.g. increased prevalence of gastrointestinal reflux disease, hiatus hernia). Furthermore, bioequivalence studies are invariably performed according to strict regulatory protocols. For example, it is unlikely that the bioequivalence data obtained in subjects who were fasted for 4 hours after dosing can be reliably extrapolated to patients who fasted for only 30 minutes post-dose, as is the dosing instruction.

We acknowledge that these arguments may be equally relevant to the originator product and do not wish to address the issue of regulatory requirements for the approval and registration of generic drugs. We do, however, need to take cognisance of these scientific concerns when a clinical choice between two drugs is required – one with no scientific data and one that has been used in numerous RCTs involving more than 20 000 subjects over more than a decade.

8. In summary, NOFSA wishes to express its concern that available information on generic alendronate may not be sufficient to determine its long-term efficacy and safety. In particular, NOFSA’s concerns relate to: (i) the extremely poor intestinal absorption and rapid skeletal uptake of bisphosphonates, which complicate their accurate quantification in blood (therefore necessitating assays on urine specimens) and the correct interpretation of bioequivalence studies; and (ii) their pre-systemic gastrointestinal side-effect profile (which is not influenced by bioequivalence).

NOFSA has taken note of the fact that the South African Medicines Control Council expresses similar concerns and has placed alendronate on its non-substitutable list. We furthermore need to take cognisance of the fact that the response to osteoporosis therapy in practice (e.g. radiological detection of fractures, changes in BMD) cannot be assessed in the short term, but takes years to evaluate.

9. In conclusion, the Foundation reiterates its commitment to improving the care of patients suffering from osteoporosis. It supports attempts to reduce pharmaceutical costs, providing that such reduced costs do not compromise patient safety or the efficacy of treatment. It wishes to emphasise the need for and support of further scientific deliberation, including clinical studies on the efficacy and safety of generic bisphosphonates before endorsing their long-term use (by health care professionals including the health funders) in the management of osteoporosis.