Strontium Ranelate is an oral preparation that is a new entrant into the armamentarium of drugs licenced for osteoporosis treatments. It is different in its mode of action by being a dual action bone agent (DABA) with properties of increasing bone formation and reducing bone resorption. These actions are in contrast to commonly used antiresorptive agents such as the bisphosphonates and selective estrogen receptor modulators which act predominantly by inhibiting osteoclast activity. Increased bone resorption is a characteristic feature of post-menopausal bone loss and this together in combination of other risk factors including a low bone mass predisposes to developing osteoporosis. Treatments currently available reduce the progression of disease by altering bone turnover, slowing bone loss and enabling normal bone formation to take place. Teraparatide (synthetic PTH) like strontium is another DABA, but its mode of delivery (subcutaneous) and limited duration of treatment, puts it into a different category from this oral preparation, taken daily on a regular long-term basis. *In vivo and in vitro* studies in animal models show that it increases bone formation by stimulating pre-osteoblast replication leading to increased bone matrix synthesis and decreases bone resorption by inhibiting osteoclast activity and differentiation. The direct dual action properties for strontium ranelate have been demonstrated entirely in a variety of animal models which have given a good understanding of the mechanisms of action. However the dynamic changes in the human studies have been by using surrogate markers such as biochemical bone turnover markers, rather than by histomorphometry on repeated bone biopsies.

Assessment of the place of this technology in current practice is therefore determined by large phase 2 and phase 3 clinical trials. One of the main features in its mode of action demonstrating anabolic properties is altering bone turnover in favour of increased bone formation biochemical markers as well as increasing bone density measurements. In the Strontium Ranelate for the Treatment of Osteoporosis Study (STRATOS) there was a 7.3% increase in spinal and 3.05% increase at the hip, bone mineral density. In the Spinal Osteoporosis Intervention trial (SOTI), there was a
41% reduction in fracturing in those with a previous vertebral fracture, together with increase in spinal and hip BMD\(^3\) of a similar magnitude to the previous study. In another study, the Treatment of Peripheral Osteoporosis Trial (TROPOS), there was a 16% decrease in non-vertebral fractures and 36% decrease in hip fractures in patients aged 74 years and over\(^4\). Overall these results are broadly similar in fracture prevention outcome from those of the bisphosphonates, the differences being in design of the studies. The SOTI study demonstrated efficacy in secondary prevention of osteoporotic fractures in patients with at least one pre-existing vertebral fracture. In the TROPOS study the age group was over 74 years. These two features make it ideally suited to be added to the list of agents recommended by NICE\(^5\) as a first line treatment for secondary prevention of osteoporotic fractures in elderly postmenopausal women.

From the patient’s perspective, the advantages of this treatment is the ease of administration, as a 2gm sachet, dissolved in a glass of water, taken at night with no additional precautions, as required for the bisphosphonates. Although the impressive increases in BMD early on could be a useful for demonstrating compliance and reassuring the patient on the efficacy of treatment, this in practice could be a problem since a substantial increase in BMD (upto 50%) is due to amplification of bone density measured by DXA by strontium itself being in Group II, the same as calcium in the periodic table. Therefore if repeat measurements are required at any time for follow-up, adjustment factors have to be employed to account for this amplification.

For the patient there are three main disadvantages of this treatment. The first is its side effect profile, such as diarrhoea, which although described as transient but lasting upto 3 months, in clinical experience, this is of concern to the patients who discontinue and rarely persevere until symptoms abate. The second side effect is the more serious venous thrombolic events (VTEs), which are reported to occur with an annual incidence of approximately 0.7% with no explanation as to why this happens. There appears to be no way to identify susceptible individuals, such as previous VTEs either due to clotting deficiencies or HRT. Vigilance in reporting suspected adverse drug reaction to the Committee of Safety of Medicine will be important in monitoring overall safety of its use in the general population and outside the close scrutiny of study conditions. The third problem, is of interference of Strontium with
measurement of serum total calcium in the serum, using conventional colourimetric assays routinely used in the laboratory. Preliminary studies of our own indicate that this interference would be about 0.25mmol/L, which would be significant if the patients calcium levels were outside the reference range at the outset. This could result in the patient being either under or over investigated for calcium disorders due to a spurious drug interference. The manufacturers recommend re-measuring calcium by an alternate method such as Induction-Coupled Plasma Emission Mass Spectroscopy (ICPMS), if drug interference is suspected. Most diagnostic laboratories in the country do not have this specialised and sophisticated technology and interference may not be suspected as the cause thereby subjecting the patient to unnecessary over-investigations. Additional studies are being undertaken by Servier to determine the extent of interference caused by strontium with serum calcium in its use in the routine clinical setting and guidance on how to manage these patients is expected to be forthcoming to clarify how to manage patients on this form of treatment.

Based on the published large scale studies in elderly post-menopausal women, Protoleos could be recommended as a first line drug in secondary prevention of osteoporotic fractures in elderly women. The anabolic properties of this agent on the bone would have obvious advantages in restoring bone density at a time when fragility fractures are common. However, in younger post-menopausal women, when increased bone resorption is a predominant factor causing net bone loss, the weakly antiresorptive properties of this agent has less obvious advantages. Since this drug is not metabolised and has direct action on bone, mild renal or hepatic impairment are not contraindications to its use in patients with secondary causes for osteoporosis.

REFERENCES:

5. NICE : TECHNOLOGY appraisal Guidance 87 (Jan 2005)