Interim Clinical Commissioning Policy Statement: Teriparatide for Osteoporosis in Men (Adults)

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Contents

1 Plain Language Summary

Osteoporosis is a condition affecting the bones which causes them to lose their strength and increases the chances of them breaking.

Women who have completed the menopause are at the highest risk of developing osteoporosis but it also affects a significant number of men. Lack of awareness of the disease in men can lead to a delay in diagnosis and treatment.

Current treatments for osteoporosis strengthen the bones and reduce the risk of a fracture taking place. Most drugs work by slowing down the breakdown of bone or increasing the cells that build new bone.

Teriparatide is a drug that works by increasing the formation of bone and so reduces the risk of fractures. It is recommended for people who have had several fractures despite having tried other drug treatments. Currently the drug is commissioned for use in women but not in men.

2 Background

A review of the current commissioning arrangements for the treatment of osteoporosis has demonstrated that there is no mechanism by which men with the most severe forms of osteoporosis are able to access teriparatide.

Teriparatide is the most effective available treatment for this patient group. It is available to women but not men and this is example of an inequality based on gender, which is a protected characteristic as defined by legislation. Although NICE will be developing guidance on non-bisphosphonate treatment of osteoporosis there is currently no timetable for the development or publication of this guidance.

Osteoporosis is a common systemic skeletal disease characterised by compromised bone density and quality, predisposing to an increased risk of fracture [NIH Consensus Statement (2000)]. Definitive clinical diagnosis requires measurement of bone mineral density (BMD). The current reference diagnostic standard is dual-energy x-ray absorptiometry (DXA) of the hip [Kanis et al 2000]. Osteoporosis is conventionally diagnosed when BMD values lie 2.5 standard deviations or more below the young adult reference age, i.e. a T-score less than -2.5. Studies suggest that about 20% of all western women over the age of 50 years have osteoporosis and that the prevalence increases exponentially with age [World Health Organisation 1994].

The clinical impact of osteoporosis is due to the increased fracture risk and the consequent increased morbidity and mortality. Within Europe, osteoporotic fractures account for almost 2% of the burden of non-communicable disease and are associated with more disability adjusted life-years (DALYs) than common cancers, with the exception of lung cancer. The DALY's lost in Europe due to osteoporosis (2.0 million) are greater than for rheumatoid arthritis (1.0 million). Osteoporosis increases the risk of bone fracture at all sites, but typical 'low-trauma' fractures occur at the distal forearm, humerus, vertebrae and hip. It has been estimated that nearly one woman in two will experience an osteoporosis related fracture following menopause [Chrischilles et al1991].

In developed nations, around one in three women and one in five men aged 50 years or more will suffer a fragility fracture during their remaining lifetime. In the UK, around 536,000 people suffer fragility fractures each year, including 79,000 hip fractures, with a cost in 2010 estimated at £3·5 billion, expected to rise to £5·5 billion per year by 2025 [Hernlund et al 2013]. For the individual, a hip fracture can be devastating with loss of independence and less than one third of patients make a full recovery; mortality at one year post-fracture is approximately 20% [Sernbo et al1993].

The average stay in hospital is 27 days and hip fractures account for more than 20% of all orthopaedic bed occupancy. With an aging population, the cost to society and individuals of treatment, rehabilitation and premature mortality is set to increase.

Pharmacological intervention in osteoporosis

Osteoporosis in men

Alendronate and risedronate are first line treatments in men. Where these are contraindicated or not tolerated, zoledronic acid or denosumab are the most appropriate alternatives. Teriparatide is a licensed alternative treatment for men with osteoporosis who have been exposed to other anti-fracture agents, but still have low bone density and evidence of vertebral fractures. Teriparatide is recombinant parathyroid hormone (PTH) 1-34 which is administered subcutaneously for up to two years. It is an anabolic agent whereas the majority of standard treatments act through as antiresorptive agents.

3 Commissioning Position

The current commissioning arrangements for treatment of osteoporosis do not include a mechanism by which men with the most severe forms of osteoporosis can access teriparatide.

Teriparatide is the most effective available treatment for this patient group. It is available to women but not men and this is example of an inequality based on gender, which is a protected characteristic as defined by legislation. Although NICE will be developing guidance on non-bisphosphonate treatment of osteoporosis the timetable for the publication of this guidance is 2021.

Based on a limited scoping of the evidence, NHS England has concluded that there is sufficient evidence to support for interim commissioning of this treatment for the indications and clinical criteria listed in adults.

Clinical commissioning criteria

3.1 Indications

Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in men.

3.2 Dose

The adult male dose is 20 micrograms daily for a maximum of 24 months.

3.3 Contra-indications

Bone metastases; hyperparathyroidism; metabolic bone diseases; Paget's disease; pre-existing hypercalcaemia; previous radiation therapy to the skeleton; skeletal malignancies; unexplained raised alkaline phosphatase.

3.4 Exclusions

Severe renal impairment.

Caution should be exercised in moderate renal impairment.

Paediatric patients (less than 18 years), or young adults with open epiphyses.

3.5 Starting and Stopping Criteria

Starting Criteria

Using the criteria in NICE TA161 as a guide, teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in men:

- who are unable to take alendronate and risedronate, or have a contraindication to or are intolerant of alendronate and risedronate (as defined in section 1.6 – see below), or who have had 'an unsatisfactory response is defined as occurring when a man has another fragility fracture despite adhering fully to treatment for 1 year and there is evidence of a decline in BMD below his pre-treatment baseline.
- who are 65 years or older and have a T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, or who are aged 55–64 years and have a T-score of –4 SD or below plus more than two fractures.

Because fracture incidence is related to absolute bone density regardless of gender it is important that this is taken into account when calculating fracture risk. Accordingly, T-scores used for fracture risk calculation in men should be based on the National Health and Nutrition Examination Survey (NHANES) female reference database. The online version of the FRAX Fracture Risk Assessment Tool does this automatically if absolute bone mineral density is entered and the manufacturer of the densitometer specified.

In line with the NICE guidance, intolerance of alendronate or risedronate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly. Furthermore, the NICE guidance states an unsatisfactory response is defined as occurring when there is another fragility fracture despite adhering fully to treatment for one year and there is evidence of a decline in BMD below her pre-treatment baseline.

Stopping Criteria

Treatment may be stopped if the patient has adverse reactions. The maximum total duration of treatment with teriparatide should be 24 months. The 24-month course of teriparatide should not be repeated over a patient's lifetime.

4 Effective from

This policy is effective from the date of publication.

5 Evidence Summary

NHS England has considered the evidence submitted as part of the preliminary policy proposal to establish the interim clinical commissioning policy statement, including the clinical criteria for initiating and discontinuing the intervention. This includes up to three of the most clinically impactful publications, identified using a literature search strategy defined by the clinical lead. These publications are summarised below.

Publication 1

Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. (2001) 'Effect of Parathyroid Hormone (1-34) on Fractures and Bone Mineral Density in Postmenopausal Women with Osteoporosis' New England Journal Med. May 10; 344(19), pp.1434-41

A randomised controlled trial assigned 1637 postmenopausal women with prior vertebral fractures to either 20 or 40 µg of teriparatide or placebo. The study was sufficiently powered to demonstrate significant differences in bone density between placebo and teriparatide treated patients. Median duration of observation was 21 months. In the 20 µg treatment group there was a 65% reduction in the risk of one or more new vertebral fractures, 53% less likely to have one or more new non-vertebral fractures. Bone density increased by 9% at the lumbar spine and by 3% at the femoral neck in the 20 µg per day treatment group.

11% of women in the 40µg group, 6% of women in the 20 µg group and 6% of women in the placebo group withdrew from the study due to an adverse event. The most commonly reported adverse events were nausea, headache and dizziness. No cases of osteosarcomas were reported. The authors concluded that treatment of postmenopausal osteoporosis with parathyroid hormone 1 – 34, teriparatide, decreases the risk of vertebral and non-vertebral fractures; increases vertebral, femoral and total body bone mineral density; and is well tolerated.

The strength of the study was the scale and power statistically to identify clinically meaningful change in terms of fracture risk reduction. The limitation of the study design was that it did not include men.

Publication 2

Orwoll ES, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, Kaufman JM,

Clancy AD, Gaich GA. (2003) 'The Effect of Teriparatide [Human Parathyroid Hormone (1-34)] Therapy on Bone Density in Men With Osteoporosis' Journal of Bone and Mineral Research Volume 18, Number 1.

This study aimed to extend the observations in women to determine whether equivalence was demonstrated in terms of bone density in men. In total, 437 men with low bone density (2 SD below young adult male mean) at the hip or spine were randomised to either placebo, teriparatide 20 µg or 40µg. The study ran for 11 months in total. Surrogate markers for fractures were analysed including bone mineral density. At the end of the study, bone mineral density had increased by 5.9% at the spine ($p<0.001$) and 1.5 % at the femoral neck for the 20µg group ($p=0.029$).

Adverse events were similar in the 20µg and the placebo group. The most common reported adverse effects were nausea and headache. There were no cases of osteosarcoma. The authors concluded that the positive bone mineral density responses to teriparatide in men highlighted its potential utility as a therapy for men with osteoporosis.

The strength of this study is that it was a large scale study in men looking at surrogate markers for fracture, (positive) changes in bone mineral density. The limitation of the study is that it was of relatively short duration and was not powered to demonstrate incident fractures. The population studied was predominantly Caucasian which may limit the wider applicability to other ethnic groups.

Publication 3

Niimi R, Kono T, Nishihara A, Hasegawa M, Matsumine A, Kono T, Sudo A. (2015) 'Analysis of Daily Teriparatide Treatment for Osteoporosis in Men' Osteoporosis International 26:1303–1309

This was a retrospective study comparing the effects of daily teriparatide treatment in postmenopausal women with osteoporosis and men with osteoporosis. Markers of drug effect including changes in bone mineral density and changes in bone turnover markers were analysed. The study population was 488 women and 75 men.

All patients received the standard teriparatide dosage of 20 µg per day and study observations were made for the first 12 months. In men, the percentage change in lumbar spine bone density rose significantly by 11.3% and the femoral neck bone density increased by 0.4% at 12 months. In postmenopausal women, the percentage change in lumbar spine bone density increased by 9.6% at the spine and by 2.4% at the femoral neck at 12 months.

The percent and absolute bone density increases in lumbar spine and femoral neck between men and women were similar. Using P1NP as a bone turnover marker, the authors show that the absolute increases in this marker at four, eight and 12 months were similar in men and women. The authors concluded that daily teriparatide treatment was as effective in men as in postmenopausal women regardless of sex differences when analysed according to bone turnover markers and bone mineral density change.

The strength of this study is that there is a direct comparison between the effects of teriparatide in men and women, demonstrating no significant change according to

sex. The limitation of the study is that only bone turnover markers and bone density was feasible to measure and there are no clear fracture outcome data.

6 Cost

The cost of implementing the clinical commissioning policy statement is driven by both the cost of teriparatide together with the cost of delivery. Drug costs have been derived using the lowest acquisition costs. Having taken into account the clinical presentation, the teriparatide biologic with the lowest acquisition costs should be used. This is likely to be a teriparatide biosimilar. The cost of delivering care reflects appropriate national prices, as stated within the National Tariff Payment System.

7 Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Review of current commissioning of treatment for osteoporosis has demonstrated that there is no mechanism by which men with the most severe forms of osteoporosis are able to access teriparatide which is the most effective treatment. This is a manifest example of discrimination based on gender (a protected characteristic).

8 Mechanism for funding

Teriparatide will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the provision of specialised endocrinology and specialised rheumatology services. Having taken into account the clinical presentation, the teriparatide biologic with the lowest acquisition costs should be used. This is likely to be a teriparatide biosimilar.

9 Responsible CRGs

Specialised Endocrinology and Specialised Rheumatology.

10 Date approved

June 2018

11 Policy review date

This is an interim policy that will be superseded when a NICE Technology Appraisal is published.

12 Links to other Policies

The Clinical Commissioning Policy: Teriparatide for the treatment of osteogenesis imperfecta (Adults) Reference: NHS England: 16002/P remains extant.

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