SOUTH EAST LONDON

OSTEOPOROSIS TREATMENT PATHWAY

Guideline Summary

This clinical guideline outlines the treatment pathway for adult patients with Osteoporosis

This guideline incorporates some of the recommendations from SIGN, NICE, National Osteoporosis Guideline Group (NOGG) and local expert opinion. It adopts a pragmatic approach to assess patients' risk of fracture in conjunction with the use of bone mineral density (BMD) measurement

This guideline was developed by the osteoporosis treatment pathway short life task and finish group part of the SEL Integrated Medicines Optimisation Committee

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1. Executive Summary

This guideline provides a standardised, evidence-based approach for the **assessment and treatment of adult patients with osteoporosis** across primary and secondary care in South East London; with the aim to improve fracture prevention, optimise treatment choices, and ensure equitable access to care.

Key Recommendations

1. **Fracture Risk**
    - Osteoporosis is diagnosed clinically, often supported by dual-energy X-ray absorptiometry (**DEXA) scans** and **Fracture Risk Assessment Tool (FRAX) scores**
    - Diagnosis can be made without DEXA in high-risk individuals (e.g., elderly with low-trauma fractures)
    - Risk factors include **modifiable** (e.g., smoking, low BMI) and **non-modifiable** (e.g., age, previous fracture) factors, as well as **co-existing diseases** and **medications**

2. **Vitamin D and calcium supplementation**
    - **Calcium and Vitamin D** are not standalone treatments for the management of osteoporosis and **should not be regarded as adequate for either treatment or prevention of osteoporosis**
    - There is little evidence that calcium and vitamin D supplementation alone substantially reduces fracture incidence, although increased dairy intake (which also increases protein intake) may reduce fracture and falls risk, in particular for individuals in residential care
    - Sufficient calcium intake and vitamin D levels help to prevent the risk of hypocalcaemia with anti-resorptive therapy. Supplementation in this circumstance should consider existing dietary intake and serum levels

3. **Pharmacological management**
    - Anabolic treatment (biosimilar teriparatide, abaloparatide, or romosozumab) is the preferred treatment option where appropriate for individuals with a very high fracture risk (primary or secondary prevention of osteoporosis), based on consistent results from head-to-head trials with antiresorptive agents.
    - Anabolic treatment should be followed by antiresorptive treatment.
    - Denosumab treatment should not be delayed or stopped without careful consideration of subsequent bone protection.

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South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London Integrated Care System: NHS South East London (covering the boroughs of Bexley/Bromley/Greenwich/ Lambeth/Lewisham and Southwark) and GSTFT/KCH /SLaM/ Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

2. Scope

This treatment pathway applies to adult patients with a diagnosis of osteoporosis, including post-menopausal women, pre-menopausal women and men.

The pathway is set out to guide the treatment options available for primary and secondary prevention of osteoporosis across non-specialist and specialist providers.

3. Rationale

This treatment pathway provides an evidence-based approach for the management of osteoporosis across primary and secondary care, whilst maximising cost-effectiveness and clinical outcomes. The aim is to standardise care across South East London and ensure equitable access to treatments.

4. Background

Osteoporosis is the most common disease of ageing, and the most common chronic bone disease. It is characterised by the loss of bone tissue, accompanied by structural changes, leading to a loss of bone strength and an increased risk of fracture. Osteoporosis results from an imbalance between formation of new bone and resorption (breakdown) of existing bone. In a person with osteoporosis, the bones become porous and fragile, losing density and strength. Osteoporosis typically develops over a long period of time and is often referred to as a "silent disease" because it progresses without obvious symptoms or signs - until a fracture occurs. Fractures caused by osteoporosis are termed low-trauma (sometimes termed, 'fragility') fractures and occur following even minor stresses such as a trip, bending over, coughing, or lifting. The formal definition of a low-trauma fracture is one that occurs after a fall from standing height or less. The commonest osteoporotic fractures are spine, hips, and wrist; fractures of the pelvis and shoulder are also very common. A major osteoporotic fracture is a clinical spine, hip, forearm or humerus fracture. The tool has been externally validated in independent cohorts[3].

One in two women and one in five men will break a bone after age 50 years[1]; and an estimated 549,000 new low-trauma fractures occur each year in the UK (a third in men) – with population ageing, a 19.6% increase is expected by 2030[2]. Costs of fragility fractures to the NHS exceed £4.7 billion per annum, of which £2.6 billion is directly incurred after an incident fracture (£1.1 billion for hip fractures alone)[3]. As well as the burden of health and social care resources from hip and non-hip fragility fractures, the impact of fractures on individuals can be devastating, leading to loss of independence, mobility and capacity to carry out everyday tasks.

After a first fracture, affected individuals have a high (two-to three-fold) risk of another fracture, particularly within the next 12 months. 23% of second fractures in women over the age of 50 occur within one year of the first event and many of these women are not on any fracture prevention, despite their sentinel event.

Many risk factors for osteoporosis are known – both non-modifiable and modifiable. Osteoporosis is highly genetically determined and affects females more than males (due to differential pubertal growth and to menopause-induced hypogonadism) and older people more than younger people. Osteoporosis also has social determinants (low income, poor diet, reduced access to physical activity, correlation with smoking and excess alcohol); and the risk of osteoporosis is increased by many other conditions and/or their treatment (see table 4.1 below).

Osteoporosis is a clinical diagnosis based on a number of factors (most obviously, a history of low trauma fracture). Tools such as Dual Energy X-ray Absorptiometry (DEXA) scanning and Fracture Risk Assessment (FRAX – see figure 1) may be used to support the diagnosis, or to identify individuals at risk of osteoporotic fracture, enabling timely intervention including primary prevention.

Figure 1 – FRAX assessment thresholds for ten-year probability of a major osteoporotic fracture (MOF)[3]

DEXA scans give results in absolute terms (g/cm^2), noting that this is a real measurement of what is in reality a volumetric measurement; and in relative terms according to the normal curve for BMD in the general population: a T-score (a measure of bone density compared with the mean and standard deviations (SD) for young healthy adults of the same sex) and Z-scores (SD compared with the mean for an age and gender matched population).

In general Z-scores should be used when assessing bone health for younger individuals (e.g., less than 50 years old) and the utility of using T-scores to define disease states in younger individuals, who are [in general] at very low absolute risk of low-trauma fracture, is contentious.

- T-score between -1 and +2 is considered 'normal' bone
- T-score of lower than '-2.5' is termed osteoporosis.
- T scores between -1 and -2.4 is termed osteopenia. This is not a disease state, but a description of Bone Mineral Density (BMD) relative to young healthy individuals. To illustrate, by definition according to characteristics of the normal curve: 1 in 6 people will have BMD more than one SD below average at the age of 20-30 years, so will have an 'osteopenic' T score – however, only 2.5% of 20-30 year olds will have Z scores below the normal range.
- The clinical utility of identifying osteopenia depends on the individual patient (e.g., it may provide the rationale for considering bone protection in someone on high-dose steroids); but it does not necessarily require management or monitoring.

The use of BMD alone to assess fracture risk has a high specificity but low sensitivity, which relates to differences between personal risk and the distribution of BMD within the general population. Thus, although individuals with lower BMD are at highest *individual* risk for osteoporotic fractures, at

a population level most osteoporotic fractures occur in people who do not have T-score lower than -2.5 – because there are far more people with BMD above this threshold value. BMD results should not be reviewed in isolation when making the diagnosis of osteoporosis in an individual with a low-trauma fracture; it is important to also consider the individual patient factors and characteristics which are presented.

4.1 Diagnosis

➢ Who is at risk of osteoporosis?

Risk Category	Causative Factor
Non-modifiable risk factors	**Genetic determination of bone density** **Sex** **Age** **Previous fracture** **Parental history of osteoporosis** **History of early menopause (below age of 45)**
Modifiable risk factors	**Low BMI (<20kg/m²)** **Smoking (risks associated with vaping unknown)** **Low bone mineral density** **Excess alcohol intake**
Co-existing disease	**Coeliac disease** **Diabetes mellitus** **Inflammatory musculoskeletal diseases** **Inflammatory bowel disease** **Malabsorption** **Institutionalised patients with or without epilepsy** **Human immunodeficiency virus** **Primary hyperparathyroidism and endocrine diseases** **Chronic liver disease** **Neurological diseases (including Alzheimer's disease, Parkinson's disease, multiple sclerosis, stroke)** **Moderate to severe chronic kidney disease (including end stage renal failure)**
Drug Therapy *This is not an exhaustive list.*	**Oral glucocorticoids** **Anti-epileptics** **Aromatase inhibitors** **Androgen deprivation therapy** **Long-term antipsychotics (associated with hyperprolactinaemia)** **Chronic proton pump Inhibitors** **Thiazolidinediones (oral hypoglycaemic agent)**

Adapted from: *Scottish Intercollegiate Guidelines Network (SIGN)[4].*

➢ Diagnosing osteoporosis

Assessments should include:

- Past medical history with a focus on previous low-trauma fractures and other risk factors for osteoporosis *(modifiable and non-modifiable – see above list)*
- Lifestyle history with focus on smoking cessation, safe alcohol consumption, and weight-bearing activity
- Falls risk *(falls history, screen of vision, balance, MSK disease, L&S BP, peripheral neuropathy)*
- Frailty assessment *(Timed Up and Go test [TUAG] or grip strength, Clinical Frailty Scale [CFS])* and cognitive screen *(concordance, higher level balance problem)*
- FRAX (or other fracture calculator) score *(especially for primary prevention)*

Diagnosis is clinical, largely based on assessment of risk factors and previous fracture history. DEXA scanning may help in establishing the diagnosis or when considering specialist treatments, but it is not a requirement for diagnosis or starting treatment. For example, osteoporosis can be confidently diagnosed and treated without DEXA in the following situations:

- Postmenopausal women >64 years old with vertebral compression fractures, in the absence of a pertinent history of trauma
- A neck of femur (NOF) fracture in a >74 year old
- A low-trauma fracture in nonagenarian (person above 90 years old) or in a person living with moderate to severe frailty (CFS ≥6)

➢ Investigations

There is no diagnostic blood test for osteoporosis. However, bloodwork analysis may help identify potential contributing causes/mimics and will inform personalised planning of pharmacological treatments. This is usually carried out by initiating clinician.

Baseline bloodwork may include:

- Renal profile
- Bone profile, vitamin D level, and PTH
- Liver function tests
- TFTs and coeliac screen
- ESR and FBC

If ESR is raised without straightforward explanation, especially in older individuals i.e. those >75 years old, a myeloma screen may be indicated.

A DEXA scan is frequently undertaken in the diagnostic work-up of osteoporosis, but it is not always required for diagnosis.

4.2 Glucocorticoid-Induced Osteoporosis

In individuals starting therapeutic glucocorticoids , the highest rate of bone loss occurs within the first 3-6 months of starting steroid treatment; and bone loss decreases rapidly after steroid cessation[6]. When considering bone protection in individuals on oral steroids (minimum steroid course length – 3 months), some nuances in treatment choice might be appropriate. For example, in someone starting a 3 - 6 month course of steroids, risedronate (a powerful but short-acting bisphosphonate) might be the best option. In contrast, in someone in whom the course of steroid is likely to be 1 - 2 years, a dose of zoledronic acid early after treatment commences might be a good option.

Initiation of bone-protective treatment is recommended (at the same time as glucocorticoid initiation, without waiting for a DEXA scan to be performed) in the following people commencing glucocorticoids for three months or longer:

- Women and men aged 70 years or older prescribed oral steroids at any dose
- Postmenopausal women of any age, and men aged 50 – 70 years or older, if starting the equivalent of 7.5mg/day or greater of prednisolone
- Postmenopausal women of any age, and men aged 50 – 70 years or older, with a FRAX probability of a major osteoporotic fracture/ hip fracture exceeding the intervention threshold.

- Anyone with a prior low-trauma fracture prescribed steroids at any dose *(noting here that this patient cohort should already be on appropriate anti-fracture treatment)*

Patients initiated on less than prednisolone 7.5mg/ day (or equivalent) who have a FRAX probability near to, but below, the intervention threshold should have their FRAX repeated after 12-18 months with a BMD if they remain on steroids.

Treatment of younger male and female patients may be appropriate in some scenarios, particularly those with previous history of fracture. This should be initiated following advice and guidance from a secondary care specialist or by a secondary care specialist who may consider using FRAX as a tool to support decision making.

Treatment options for glucocorticoid-induced osteoporosis include:

- Alendronate (alendronic acid)/ risedronate *(weekly dosing - off-label)*
    - For those expected to be on long-term steroids (more than 3 months), plan for a treatment duration of 5 years then review
    - For those expected to be on short-term steroids (less than 3 months), consideration should be given for use of a shorter-acting bisphosphonate (e.g., risedronate), particularly in younger individuals. This should be for the duration of the steroid treatment.
    - These treatments are non-specialist and therefore should be initiated alongside or at the point of steroids being initiated and do not routinely require referral to bone specialist or equivalent
- Zoledronate (zoledronic acid)
    - For those on long term steroids, plan for a treatment duration of 6 years or longer
- Biosimilar Denosumab
    - Should typically be reserved for those expected to be on longer–term steroid treatment. Treat for 5 years and then reassess. Do not stop denosumab without initiating alternative bone protection.
- Biosimilar teriparatide *(currently the only licensed anabolic in this setting)*
    - For those on long term steroids at very high risk of fractures
    - Plan for a treatment duration of 24 months only

Please see flowchart 5.6 and 5.7 below for further information

5. Treatment Pathway

5.1 Suggested referral into specialist care for:

- Osteoporosis in premenopausal women
- Osteoporosis in men aged <60 years old
- Major osteoporotic fracture (hip, pelvis, spine, proximal humerus, or wrist) and consideration for anabolic treatment
- All individuals with a very high risk fracture risk defined by the FRAX tool
- Treatment difficulties (e.g., intolerance to both alendronic acid and risedronate, despite review of drug administration)
- Individuals who fracture after 12 months of treatment, despite good compliance
- Glucocorticoid-induced osteoporosis, if unable to be managed according to existing guidelines such as NICE CKS and National Osteoporosis Guideline Group (NOGG)

Please see flowchart 5.6 and 5.7 below for further information

5.2 Calcium and Vitamin D Supplementation[7,8,9,10, 14,15]

- Despite extremely large studies there is little evidence that supplemental calcium and/or vitamin D (individually or collectively) reduce fracture risk substantially in most individuals living in the community. **Therefore, calcium and/or vitamin D should not be regarded as adequate management for the treatment or prevention of osteoporosis.**
- There is some evidence that calcium and vitamin D may reduce fracture in individuals in residential care, particularly individuals at high risk of malnutrition. This may in fact be due to the treatment of low-grade osteomalacia, rather than osteoporosis *per se*; however, there is also good evidence that increasing dairy intake in these individuals can prevent both fractures and falls.
- In individuals receiving antiresorptive drugs, usual clinical practice is to ensure sufficient calcium intake and vitamin D levels (e.g., to avoid hypocalcaemia). Here 'sufficient' means a calcium intake >1g/daily and vitamin D level of >50nmol/L (and >70nmol/L before going into winter).
- There is little evidence of additional benefit for giving calcium in individuals with excellent dairy intake (3-4 serves a day, equivalent to >1g daily), whether or not someone is on an antiresorptive agent. To see whether a patient is getting enough calcium from what they eat and drink, an online calcium calculator is available here. The calcium content of non-dairy products can be accessed here.
- There is little evidence of additional benefit in giving supplementary vitamin D in individuals who already have sufficient vitamin D levels, whether or not someone is on an antiresorptive agent.
- When co-prescribing vitamin D supplements with an oral anti-resorptive agent (e.g. alendronic acid or risedronate), dose will depend on prior vitamin D status. Some individuals may require a loading dose (e.g., 50,000 units weekly, for six weeks) before moving to a maintenance dose (typically, 1000-2000 IU daily).
- For patients about to start a parenteral anti-resorptive agent (e.g. zoledronic acid or biosimilar denosumab), rapid correction of vitamin D deficiency may be required (to reduce the risk of hypocalcaemia). Consider prescribing a treatment loading regimen if the vitamin D level is below 50 nmol/L, followed by regular maintenance doses. See SEL vitamin D guidelines for further information.

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5.3. Bone Turnover Markers

- Bone turnover markers (BTM) are not routinely used in simple osteoporosis care but can be a useful tool in measuring efficacy of antiresorptive medication, particularly where compliance is unclear.
- Potential areas of further utility are in prediction of atypical femoral fractures and determining duration of bisphosphonate treatment suspension.
- Serum propeptide of type I collagen (PINP, a formation marker) and serum C-terminal telopeptide of type I collagen (CTX-I, a resorption marker) are the most commonly used BTM. P1NP has lower circadian rhythm and is less affected by food intake, compared with CTX. P1NP is therefore often the preferred BTM in clinical practice as translation to the primary care setting is uncomplicated.
- All BTMs are elevated after recent fracture and therefore levels are difficult to interpret in the immediate post fracture period (pragmatically, up to a year).

5.4 Repeat DEXA Scan

DEXA scans are sometimes repeated after a course of osteoporosis treatment (for detailed rationale please see NOGG guidance for more information). However, treatments are designed to reduce risk of further fracture, and the observed reduction in fracture risk with appropriate treatments for osteoporosis (typically, 50-60% for vertebral fracture and 30% for non-vertebral fractures) is much greater than BMD change (typically 1-2% per annum with bisphosphonates, mainly due to excess mineralisation in bone with reduced turnover). Therefore, DEXA scans should only be undertaken if the result will change management. For most individuals, there is little reason to repeat DEXA until at least five years after starting treatment.

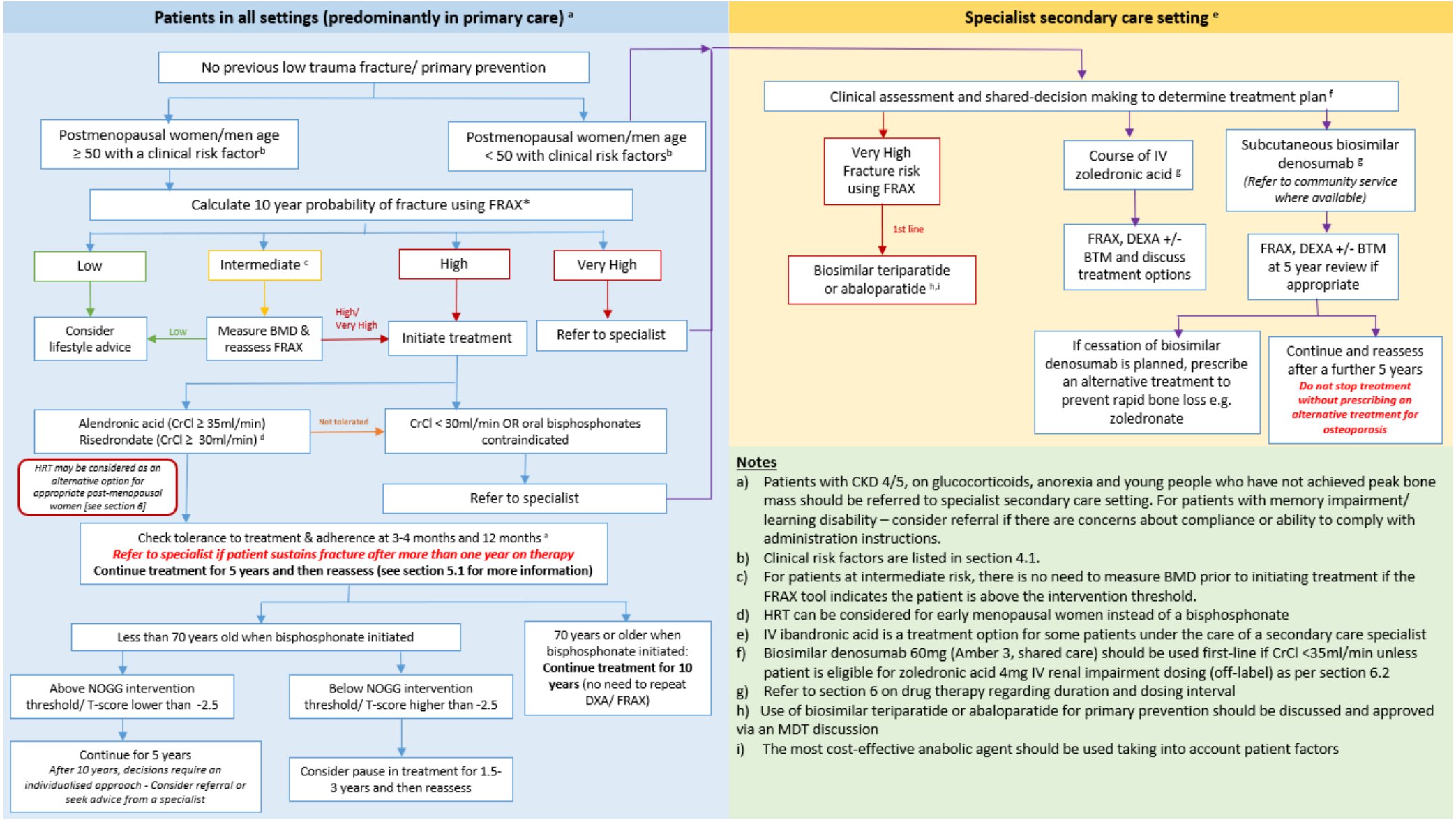
Relatedly, it is generally inappropriate to repeat a DXA scan more often than every two years, due to the relatively high coefficient of variation (CV) of DXA affecting capacity to detect least significant change (with a clinically-significant change in BMD usually considered to be 5 %). This should not be misinterpreted as meaning that BMD has to be measured every two years.

5.5 Overprescribing Considerations

All patient encounters present an opportunity for potential deprescribing of medications as part of personalised care, reflecting changes in treatment burden, symptoms, risk and benefits and patient choice.

Due to the long action of some bisphosphonates (zoledronate, alendronate), pauses in osteoporosis treatment can be considered in some circumstances , reducing burden of treatment at intervals (see section 5.6, 5.7 and section 6 for more information). Further information is available via the Royal Osteoporosis Society. Calcium +/- vitamin D replacement may be appropriate in individuals receiving specific osteoporosis therapy (such as antiresorptive therapies in individuals in residential care and at high risk of deficiency). However, there is no evidence for prescribing calcium/vitamin D in isolation as meaningful options for fracture reduction in the general community

5.6 Primary Prevention of Low Trauma Fractures



Notes

a) Patients with CKD 4/5, on glucocorticoids, anorexia and young people who have not achieved peak bone mass should be referred to specialist secondary care setting. For patients with memory impairment/ learning disability – consider referral if there are concerns about compliance or ability to comply with administration instructions.
b) Clinical risk factors are listed in section 4.1.
c) For patients at intermediate risk, there is no need to measure BMD prior to initiating treatment if the FRAX tool indicates the patient is above the intervention threshold.
d) HRT can be considered for early menopausal women instead of a bisphosphonate
e) IV ibandronic acid is a treatment option for some patients under the care of a secondary care specialist
f) Biosimilar denosumab 60mg (Amber 3, shared care) should be used first-line if CrCl <35ml/min unless patient is eligible for zoledronic acid 4mg IV renal impairment dosing (off-label) as per section 6.2
g) Refer to section 6 on drug therapy regarding duration and dosing interval
h) Use of biosimilar teriparatide or abaloparatide for primary prevention should be discussed and approved via an MDT discussion
i) The most cost-effective anabolic agent should be used taking into account patient factors

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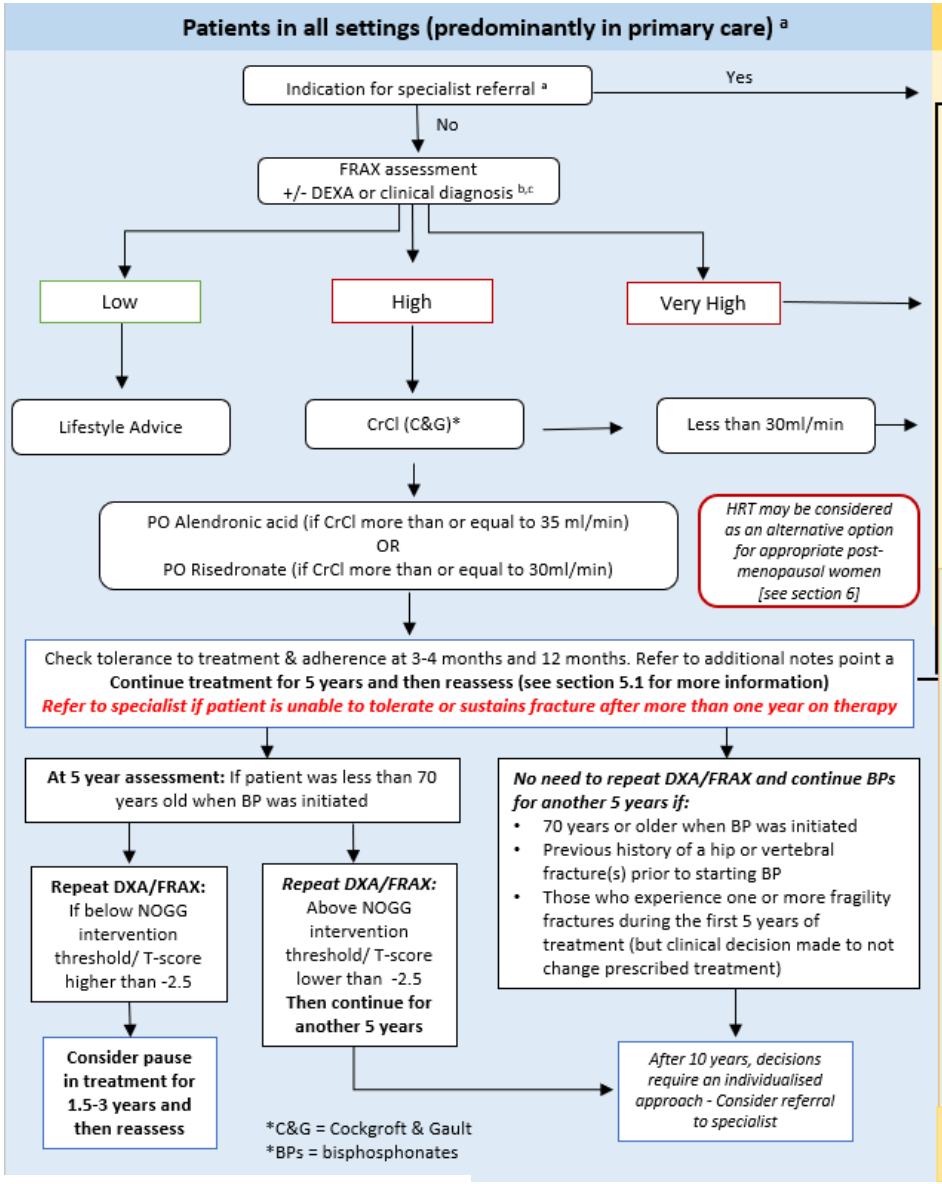
5.7 Secondary Prevention of Fragility Fracture



Specialist secondary care setting

Major osteoporotic fracture & high or very high fracture risk → DEXA if required for treatment decision

Clinical decision /patient choice
(Noting that oral bisphosphonates may be appropriate for some individuals)

***Table A (assuming oral treatments/HRT are inappropriate [d, e]**
Treatment options in no order of preference

IV zoledronic acid	Subcutaneous biosimilar denosumab	Subcutaneous biosimilar teriparatide	Subcutaneous romosozumab *postmenopausal women only	Subcutaneous abaloparatide *postmenopausal women only
All patients *see further information (including patients with renal impairment) in Section 6.2*	All patients Denosumab can be prescribed in non-specialist settings in line with Amber 3 (shared care) formulary categorisation *see further information in Section 6.3*	Consider in all patients that meet locally approved criteria *See full criteria in additional notes section*	1) Severe osteoporosis 2) Major osteoporotic fracture in last 24 months *see further information in Section 6.5*	*Patients at very high risk of fracture* *see further information in Section 6.6*

Additional Notes

a) Referral to specialist secondary care setting:
Patients with a major osteoporotic fracture within 24 months or history of 2 or more vertebral fractures and at very high risk of fracture.
Patients with CKD 4/5, patients on long-term steroids treatment equivalent to prednisolone 7.5 mg/day, anorexia and young people who have not achieved peak bone mass. Consider referral for patients if there are concerns about compliance or ability to comply with administration instructions, for example patients with a learning disability or dementia.
If an individual fractures after at least 12 months of treatment, they may be eligible for anabolic treatments, so should be considered for specialist referral.
b) Clinical risk factors are listed in Section 3.1.
c) If there is clear evidence of Osteoporosis without a DXA scan i.e. presence of fragility fractures in presence of clinical risk factors, do not delay treatment.
d) Ibandronic acid is a treatment option for some patients under the care of a secondary care specialist
e) Refer to section 5 on drug therapy regarding duration and dosing interval
f) Refer to Section 4.2 for more information on glucocorticoid-induces osteoporosis
g) For switching treatment e.g. new fragility fractures on treatment, adverse drug reactions, new contraindication: specialist to consider alternative treatment options available as per Table A

Biosimilar teriparatide eligibility in SEL *(outside of NICE guidance & NHSE commissioning policy)* – **see section 6.4**

- Post menopausal women and men with osteoporosis at very high risk of fractures
- Osteoporosis associated with glucocorticoid therapy in women and men at very high risk of fracture

All treatment options in Table A should be considered; however, there should be a consideration for anabolic treatment preferentially where clinically appropriate

*Fracture Risk Assessment Tool (FRAX)

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6. Drug Information

NB. For full list of side effects, cautions and contraindications, please see the BNF and Summary of Product Characteristics. Some of these drugs are subject to MHRA alerts; please follow links below to MHRA website for further details.

6.1 Oral Bisphosphonates	
Dose	Alendronic acid – 70mg once weekly (off-label in men) (CrCl ≥ 35ml/min) Risedronate sodium – 35mg once weekly (CrCl ≥ 30ml/min) *Weekly dosing off-label for the management of glucocorticoid-induced osteoporosis*
Recommended duration of therapy	Check treatment tolerance after 12 to 16 weeks and check adherence at 1 year. Continue treatment for 5 years. At 5 years, or sooner if fracture sustained or risk factors change, reassess adherence, risk factors and treatment choice. This may include a FRAX assessment and BMD measurement. Longer durations of treatment, for at least 10 years, are recommended in the following men and women: • Age ≥70 years at the time that the bisphosphonate is started, or • Who have a previous history of a hip or vertebral fracture(s), or • Treated with oral glucocorticoids ≥7.5 mg prednisolone/day or equivalent, or • Who experience one or more fragility fractures during the first 5 years of treatment (if treatment is not changed). After 10 years, treatment decisions should be made on an individual basis. Specialist advice may need to be sought.

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Supporting information	• NICE TA 464 bisphosphonates for treating osteoporosis patient decision aid • MHRA/CHM advice - Bisphosphonates: atypical femoral fractures (June 2011) - Atypical femoral fractures have been reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis; atypical femoral fractures are considered a class effect of bisphosphonates - During bisphosphonate treatment, patients should be advised to report any thigh, hip, or groin pain. Any patient who presents with such symptoms should be evaluated for an incomplete femur fracture • MHRA/CHM advice - Bisphosphonates: osteonecrosis of the jaw (November 2009) - The risk of developing osteonecrosis of the jaw (ONJ) in association with oral bisphosphonates seems to be low. The risk of ONJ is substantially greater for patients receiving intravenous bisphosphonates for cancer indications than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease). - There is clear evidence to suggest there is bisphosphonate-specific and indication-specific risk factors for ONJ such as potency (highest for zoledronic acid); route of administration (e.g., intravenous ibandronate, pamidronate, and zoledronic acid); and cumulative dose. - A history of dental disease, including invasive dental procedures, dental trauma, periodontal disease, and poorly fitting dentures is associated with an increased risk. - All patients with cancer should have a dental check-up before bisphosphonate treatment. All other patients who start bisphosphonates should have a dental examination only if they have poor dental status. - During bisphosphonate treatment, patients should maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling of ONJ. • MHRA/CHM advice - Bisphosphonates: very rare reports of osteonecrosis of the external auditory canal (December 2015) - 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, or in patients with suspected cholesteatoma - Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma - Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during bisphosphonate treatment • **Local advice from dental bone clinic for patients receiving medication-related osteonecrosis of the jaw (MRONJ) - associated drug therapy** Permitted treatments: - Routine dental care is not contraindicated in patients treated with antiresorptive medication and may help prevent the need for dental extractions. - Scaling and root planing

	- Routine restorations - Placement of crowns and bridges - Root canal treatment - Use of local anaesthesia as necessary <u>Procedures to be avoided whenever possible:</u> - Oral/periodontal surgery that exposes or manipulates bone. Oral surgery and implants in patients receiving MRONJ-associated drug therapy require specialist management so please refer the patient to the oral surgery/maxillofacial department for further assessment.

6.2 Zoledronic acid (Red – hospital only)

Dose	**Licensed dosing:** 5mg given intravenously every 12 months. **Extended dosing interval (off-label)**[11,12,13]: Alternatively, on specialist advice, the dosing interval with zoledronic acid 5mg intravenously may be extended up to 18 months in the **non-hip fragility fracture population** i.e., 3-4 doses administered over up to 4.5-6 years. As per SIGN guidance, the following patients may be suitable for extended interval dosing: • Primary prevention: 1. Age ≥ 65 years 2. 10-year risk ≥10% 3. DXA scan: T score -1.0 to -2.5 (if clinically appropriate or available) • Secondary prevention: 1. Age ≥ 65 years 2. DXA scan: T score -1.0 to -2.5 (if clinically appropriate or available) **It is increasingly clear that a lower dose and longer spacing between zoledronic acid treatments can still provide excellent fracture protection for women with osteopenia[12] and men and women with osteoporosis[13]. There is extremely similar reduction in fracture and improvement in BMD - whilst acknowledging not head-to-head comparisons[12].** It is not the intention of this document to be overly prescriptive regarding exact dosing and dosing intervals, as all treatment decisions are individualised, patient-centered and based on previous treatment success (e.g., BMD, frailty, dementia, residential care considerations, contemporaneous glucocorticoid use, etc.). Using bone turnover markers to guide dosing frequency may be a reasonable means of tailoring personalised approaches in individual patients, at the clinician's discretion.

	Excellent fracture prevention has been shown with longer dosing intervals (e.g., 5mg every eighteen months, over six years[11]) and even after a single 5mg dose. For example, extremely similar fracture reduction and BMD improvement over three years was seen after a single dose of zoledronate, compared with annual dosing for three years[12,13], acknowledging this was not a head-to-head comparison. As an example of individual tailoring of these off-label options, a single dose may be appropriate to provide appropriate fracture protection for a frail elderly individual with life expectancy less than 3 years; if the individual survives longer than expected another dose could then be considered.
	Renal Impairment dosing: off- label (CrCl 30 – 35 ml/min or eGFR >30 ml/min/1.73m² in selected patients) – see formulary recommendation 165 for further information
	• The following groups of patients are eligible for treatment with zoledronic acid 4mg intravenously every 18 months (see "Extended dosing interval" section above for duration of therapy)
	  ○ Primary and secondary prevention of fragility fracture as per section 5.6 and 5.7 OR
	  ○ First line treatment for secondary prevention of a fragility fracture following a hip fracture in line with NOGG guidelines
	• Patients with limited life expectancy of 6 – 12 months are also eligible for treatment with zoledronic acid 4mg intravenously **as a single dose**
	• Zoledronic acid 4mg should ideally by administered intravenously over 30 – 60 minutes

Recommended duration of therapy	3-6 years (or 3 doses for patients on extended dosing intervals) and then re-assess fracture risk. For patients on 12 monthly dosing schedules, longer durations of treatment, for at least 6 years, are recommended in the following men and women: • Age ≥70 years at the time that the bisphosphonate is started • Who have a previous history of a hip or vertebral fracture(s) • Treated with oral glucocorticoids ≥7.5 mg prednisolone/day or equivalent • Who experience one or more fragility fractures during the first 3 doses of treatment (if treatment has not changed). Clinical review to re-assess fracture risk after 3 doses; review sooner if fracture sustained during treatment or risk factors change (e.g., start glucocorticosteroids). This may include repeat DXA scan (see NOGG guidelines for further information).
Supporting information	**Post hip fracture** Zoledronic acid is recommended first line anti-resorptive post hip fracture for suitable patients. In line with licensing, it is recommended to wait at least two weeks after hip fracture repair, although it is acknowledged that due to reasons of practicalities, it may be given earlier as patients must be provided infusion prior to discharge. Importantly, many individuals with hip fracture are given IV iron infusions, which is associated with a high prevalence of hypophosphataemia (particularly iron carboxymaltose). Appropriate monitoring of calcium and phosphate should be considered if co-prescribing of IV iron infusions and bisphosphonates. **MHRA/CHM advice: Denosumab (Xgeva™ and Prolia™); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk (July 2015)** The risk of osteonecrosis of the jaw should be explained to patients and the precautions to take; patients should be advised to:

	• tell their doctor if they have any problems with their mouth or teeth before starting treatment; if they wear dentures, they should make sure their dentures fit properly before starting treatment • maintain good oral hygiene and get routine dental check-ups during treatment • tell their doctor and dentist that they are receiving biosimilar denosumab or an intravenous bisphosphonate if they need dental treatment or dental surgery • tell their doctor and dentist immediately if they have any problems with their mouth or teeth during treatment (e.g. loose teeth, pain, swelling, non-healing sores or discharge)

6.3 Biosimilar denosumab (Osvyrti®) (Amber 3 – shared care)

Dose	60mg subcutaneous injection every 6 months
Recommended duration of therapy	Current evidence shows safety and efficacy are maintained for at least 10 years of treatment
Supporting information	**Osvyrti® is the preferred biosimilar denosumab 60mg brand in SEL** **Recognised risk of hypocalcaemia** • Biosimilar denosumab is contraindicated in patients with hypocalcaemia; this should be corrected before starting treatment • Risk of post dose hypocalcaemia increases in patients with a CrCl of less than or equal to 30ml/min; check serum corrected calcium level two weeks after each dose • Patients established on haemodialysis or peritoneal dialysis - consider increasing monitoring frequency e.g., weekly levels for 4 weeks. • Adequate intake of calcium and vitamin D is important in all patients. **MHRA Drug Safety Update: Risk of vertebral fractures on interruption or cessation of treatment (2022):** • Biosimilar denosumab cessation leads to rapid reductions in BMD and elevations in bone turnover to levels above those seen before treatment initiation • Therefore, patients who discontinue biosimilar denosumab have an increased risk of sustaining multiple vertebral fractures. • If denosumab therapy is stopped, prescribe an alternative treatment to prevent rapid bone loss e.g. zoledronic acid after the last injection of biosimilar denosumab if suitable • If zoledronic acid is given post denosumab, bone turnover markers may be measured 3 and 6 months after administration of zoledronic acid. This can help to guide subsequent zoledronic acid infusions **Transitioning from biosimilar denosumab to anabolic therapy is not recommended. However, in line with NOGG guidance, if biosimilar denosumab therapy is stopped, IV zoledronic acid is recommended 6 months after the last injection of biosimilar denosumab, with subsequent monitoring of serum CTX guiding the timing of further treatment. Where monitoring of serum CTX is not possible, consider a further IV zoledronic acid 6 months after the first dose of zoledronate.** **Biosimilar denosumab plus teriparatide in post-menopausal women at very high risk of a second imminent fracture:** **This combination is used for a total of 24 months (the duration of teriparatide therapy). Once the teriparatide course is complete, patients should continue on biosimilar denosumab as the antiresorptive agent.** ***See section 6.2 for more information regarding MHRA/CHM advice: Denosumab (Xgeva™ and Prolia™); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk (July 2015)*** *Please see SEL biosimilar denosumab 60mg for the treatment of osteoporosis and prevention of osteoporotic fractures in adults shared care guideline for further information*

6.4 Biosimilar teriparatide (Red – Hospital only) (*local choice of most cost-effective biosimilar)	
Dose	20 microgram subcutaneous injection every day for 24 months (course not to be repeated)
Recommended duration of therapy	24 months
Supporting information	To be prescribed in the following patient groups (outside of NICE TA 161 and NHS England Clinical Commissioning policy: teriparatide for osteoporosis, however this is established practice locally): • Postmenopausal women and men aged 50 years or older where clinically appropriate with a very high fracture risk in both primary or secondary prevention of osteoporosis. • Osteoporosis associated with systemic glucocorticoid therapy in women and men with a very high fracture risk (*men and women aged 18-40 judged to be at very high risk of fractures due to systemic glucocorticoid therapy should be discussed and reviewed via a multidisciplinary team where available)* **Transient elevations in calcium:** • In normocalcaemic patients, slight and transient elevations of serum calcium concentrations have been observed following biosimilar teriparatide injection. Serum calcium concentrations reach a maximum between 4 and 6 hours and return to baseline by 16 to 24 hours after each dose of biosimilar teriparatide. Therefore, if blood samples for serum calcium measurements are taken, this should be done at least 16 hours after the most recent biosimilar teriparatide injection. **Stopping treatment:** • Initiate treatment with anti-resorptive without delay after completion of the course. This should be planned at the time biosimilar teriparatide is instigated to avoid a gap in treatment. **Homecare:** • biosimilar teriparatide is provided by a homecare service, which includes delivery of the injections and injection training if required. Patients should be deemed competent to self-administer or a suitable carer that can support a daily injection to facilitate treatment.

6.5 Romosozumab (Evenity®) (Red – hospital only)	
Dose	210mg subcutaneous injection once a month for 12 months
Recommended Duration of therapy	12 months as per NICE TA 791
Supporting information	To be prescribed in accordance with NICE TA 791 - Romosozumab for treating severe osteoporosis: • Post-menopausal women • A major osteoporotic fracture (spine, hip, forearm or humerus fracture) within the last 24 months • Severe osteoporosis which may be defined by a T score lower than - 2.5 and an osteoporotic/fragility fracture. • Patients with clinically severe osteoporosis but not reaching the T score threshold of lower than - 2.5 due to clinical scenarios such as co-existing degenerative conditions or presence of a major fracture. **Cardiovascular risk:** • Romosozumab is contraindicated in patients with a history of myocardial infarction or stroke in the last 12 months. • Carefully consider cardiovascular risk vs fracture risk over the following 12 months and ensure shared decision making with patient to come to a personalised decision. Please see QRISK3 calculator for further information regarding cardiovascular risk. **Hypocalcaemia:** • Romosozumab is contraindicated in patients with hypocalcaemia; correct before starting treatment. **Stopping treatment:** • Initiate treatment with anti-resorptive without delay after completion of the course. This should be planned at the time romosozumab is instigated to avoid a gap in treatment. **Homecare:** • Romosozumab may be provided by a homecare service, which includes delivery of the injections and injection training if required.

6.6 Abaloparatide (Eladynos®) (Red – Hospital only)	
Dose	80 micrograms subcutaneous injection every day for 18 months (course not to be repeated)
Recommended Duration of therapy	18 months as per NICE TA 991
Supporting information	To be prescribed in accordance with NICE TA 991 - Abaloparatide for treating osteoporosis after menopause: • After menopause in women, trans men and non-binary people with a very high fracture risk *Locally preferred anabolic treatment in patients with hypocalcaemia* **Orthostatic hypotension and increased heart rate** • Orthostatic hypotension and transient episodes of increase in heart rate may occur with abaloparatide, typically within 4 hours of injection. Symptoms may include dizziness, palpitations, tachycardia, or nausea, and may resolve by having the patient lie down. • Blood pressure, cardiac status and ECG should be assessed prior to beginning treatment with abaloparatide. Abaloparatide may have vasodilating effect on vascular smooth muscle and positive chronotropic/inotropic effects on cardiac muscle. Patients with cardiac disease should be monitored for worsening of their disease. If severe orthostatic hypotension or severe cardiovascular symptoms occur, the treatment should be discontinued. **Transient elevations in calcium:** • In normocalcaemic patients, transient elevations of serum calcium concentrations have been observed following abaloparatide injection. Maximum serum calcium concentrations are reached at approximately 4 hours and return to baseline by 24 hours post dose. Therefore, if serum calcium measurements are taken this should be done at least 24 hours after the injection. • Routine calcium monitoring during therapy is not required in patients unless there are additional risk factors for hypercalcaemia. **Stopping treatment:** • Initiate treatment with anti-resorptive without delay after completion of the course. This should be planned at the time abaloparatide is instigated to avoid a gap in treatment. **Homecare:** • Abaloparatide is provided by a homecare service, which includes delivery of the injections and injection training if required. Patients should be deemed competent to self-administer or a suitable carer that can support a daily injection to facilitate treatment.

6.7 Additional Treatment Options	
Intravenous ibandronic acid (Red)	This treatment option is available for treating post-menopausal women at increased risk of fracture, who do not tolerate oral bisphosphonates in line with NICE TA 464. However, IV ibandronate is not the usual first choice for parenteral bisphosphonates as although a reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established. **Please note oral ibandronate is non-formulary in SEL.**
Raloxifene	Can be prescribed to post-menopausal women in accordance with NICE TA 160 (primary prevention) and NICE TA 161 (secondary prevention)
Hormone Replacement Therapy (HRT)	HRT is an effective alternative treatment option available for post-menopausal women at increased risk of fracture. Please see NICE guideline NG23 – Menopause diagnosis and management for further information

7. Appendix

Appendix 1: Anti-fracture efficacy of approved drug treatments for postmenopausal women, and men, with osteoporosis when given with calcium and vitamin D

Intervention	vs. Placebo			vs. Another drug treatment			
	Vertebral fracture	Non-Vertebral fracture	Hip fracture	Vertebral fracture	Non-Vertebral fracture	Hip fracture	Licenced for use in Men
Romosozumab	Ib	IIb	IIb	Superior to Alendronate (Ib)*	Superior to Alendronate (Ib)*	Superior to Alendronate (Ib)*	No
Teriparatide	Ia	Ia	Ia	Superior to Alendronate (Ia) Risedronate (Ia) Denosumab (Ia)	Superior to Alendronate (Ia)	NAE	Yes
Abaloparatide	Ia	Ia	IIb	Superior to Raloxifene (Ia)	Superior to Teriparatide (Ia)	NAE	No
Alendronate	Ia	Ia	Ia	Inferior to Teriparatide (Ia) & Romosozumab (Ib)	Inferior to Teriparatide & Abaloparatide (Ia)	Inferior to Romosozumab (Ib)	Yes
Ibandronate	Ib	Ib	NAE	NAE	NAE	NAE	No
Risedronate	Ia	Ia	Ia	Inferior to Teriparatide (Ia)	Inferior to Abaloparatide (Ia)	NAE	Yes
Zoledronate	Ia	Ia	Ia	NAE	NAE	NAE	Yes
Calcitriol	IIa	NAE	NAE	NAE	NAE	NAE	Yes
Denosumab	Ia	Ia	Ia	Inferior to Teriparatide (Ia)	NAE	NAE	Yes
HRT	Ia	Ia	Ia	NAE	NAE	NAE	No
Raloxifene	Ia	NAE	NAE	Inferior to Teriparatide & Abaloparatide (Ia)	NAE	NAE	No
Strontium Ranelate	Ia	Ia	IIb	NAE	NAE	NAE	Yes

Taken from National Osteoporosis Guideline Group UK (NOGG)[3]

HRT: hormone replacement therapy
NAE: No available evidence
Ia: Systematic reviews or meta-analysis of level I studies with a high degree of homogeneity
Ib: Systematic reviews or meta-analysis with moderate or poor homogeneity
IIa: Systematic reviews or meta-analysis of level II studies
IIb: Level II studies (inappropriate population or lacking an internal control)

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