NHS
Surrey Heartlands
Clinical Commissioning Group

Assessment and Treatment Guidelines for Osteoporosis in Adults

Contents

Purpose of this Guideline 3
What is Osteoporosis? 3
Complications 3
Fracture Risk Assessment Tools 4
How to Interpret a Fragility Fracture Risk Score 4
Who should be assessed for Fragility Fracture Risk? 4
Osteoporosis Treatment Pathway for Adults - Algorithm 1 6
Pharmaceutical Management 7
First Line Treatment - oral bisphosphonates 6
Alendronic acid 70mg once weekly* or risedronate 35mg once weekly 6
Concordance 6
Adverse Effects of Bisphosphonates 8
Patients Unable to Comply with the Administration Directions 9
Contraindications and Special Precautions for the Use of Bisphosphonates 9
Unsatisfactory Response 9
Second Line Treatment - denosumab (Prolia®) 9
Denosumab (Prolia®) 60mg/mL solution for subcutaneous injection every 6 months 9
Contraindications and Special Precautions for the Use of Denosumab 12
Adverse Effects of Denosumab 12
Rare Adverse Effects of Bisphosphonates and Denosumab 13
Specialist Treatments 11
Strontium ranelate Aristo 13
How Long Should Osteoporosis be Treated For? 15
Review of Long-Term Bisphosphonate Therapy - Algorithm 2 17
Osteoporosis in Men 18
Androgen Deprivation Therapy 18
Glucocorticoid-induced Osteoporosis-NOGG Guidance 18
Aromatase Inhibitors and Osteoporosis 19
Lifestyle and Dietary Measures 20
Advice to Patients 20
Bibliography 21
Appendix 1: Local preferred calcium and vitamin D products 22

Purpose of this Guideline

To provide:

- comprehensive and practical direction for the management of osteoporosis in the primary care setting.
- evidence-based recommendations based on NICE Clinical Knowledge Summaries (CKS) Osteoporosis – prevention of fragility fractures (March 2016), NICE TA160 *Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women*, NICE TA161 *Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women*, NICE TA464 *Bisphosphonates for Treating Osteoporosis (updated July 2019),* National Osteoporosis Guidance Group, NOGG 2017 (updated July 2019) *Clinical guideline for the prevention and treatment of osteoporosis* and Scottish Intercollegiate Guidelines Network, SIGN 142 *Management of osteoporosis and the prevention of fragility fractures* (2015, revised edition published June 2020).

What is Osteoporosis?

Osteoporosis is a condition characterised by a reduction in bone mass density and structural deterioration of bone tissue predisposing a person to an increased risk of bone fragility and susceptibility to fracture. Osteoporosis is often asymptomatic and remains undiagnosed until a fragility fracture occurs. These fractures occur most commonly in the hip (proximal femur), spine (vertebrae) and wrist (distal radius) but can occur in the arm, pelvis, ribs or other bones.

Osteoporosis is defined by the World Health Organisation (WHO) as a bone mineral density (BMD) of 2.5 standard deviations or more below the average of young healthy adults as measured by dual-energy X-ray absorptiometry (DXA) applied to the femoral neck and reported as a T-score.

The diagnosis may, however, be presumed in women aged 75 years or older who have a fragility fracture if the responsible clinician feels a DXA scan to be clinically inappropriate or impractical.

A fragility fracture is defined as occurring from a fall from a standing height or less, although vertebral fractures may occur spontaneously following a routine movement such as bending or lifting. More than one in three women and one in five men will sustain one or more osteoporotic fractures.

Complications

Osteoporotic fractures can cause:

- substantial pain
- severe disability
- a reduced quality of life, about 50% of people with an osteoporotic hip fracture will no longer be able to live independently.

Additionally, hip and vertebral fractures are linked with a decreased life expectancy. Fall-related risk factors contribute significantly to the possibility of fracture and often overlap with the risk factors for osteoporosis; identification of older people at risk should always be part of an integrated approach.

Fracture Risk Assessment Tools

NICE CG146 recommends using either of the two online risk calculators, QFracture® or FRAX®. CKS recommends using QFracture® for establishing fragility fracture risk based on the evidence that it:

- has been widely validated in the UK
- is more accurate at predicting fractures than FRAX® (up to the age of 85 years)
- considers more variables than FRAX® (although it does not consider BMD).

Both tools predict the absolute risk of hip fracture and major osteoporotic fractures (spine, wrist, hip, or shoulder) over 10 years.

There is no generally agreed threshold, regarding the definition of high risk, equivalent to the 20% intervention threshold used for cardiovascular disease. QFracture is based on the risks of patients within the QResearch database for men and women separately. For women, the cut off for the top 10% at highest risk is a 10 year risk of 11.1%. For men, the cut off for the top 10% at highest risk is 2.6%.

The NOGG intervention thresholds are based on FRAX probability and thus cannot be used with fracture risk derived from QFracture or other calculators.

How to Interpret a FRAX® Fragility Fracture Risk Score

	FRAX®	
High Risk	Red Zone of Risk Chart	
Intermediate Risk	Orange Zone of Risk Chart	
Low Risk	Green Zone of Risk Chart	

Who should be assessed for Fragility Fracture Risk?

NICE recommend considering assessment of fracture risk in:

- all women over 65 years and all men over 75 years
- all women aged under 65 years and men aged under 75 years in the presence of risk factors, for example:
  - previous fragility fracture
  - current use or frequent recent use of oral or systemic glucocorticoids
  - history of falls
  - family history of hip fracture
  - other causes of secondary osteoporosis
  - low body mass index, BMI, (less than 18.5kg/m^2)
  - smoking
  - alcohol intake of more than 14 units per week for women and men.

Do not routinely assess fracture risk in people **aged under 50 years** unless they have major risk factors (for example, current or frequent recent use of oral or systemic glucocorticoids (more than 7.5mg prednisolone or equivalent per day for 3 months or longer), untreated premature menopause or previous fragility fracture), because they are unlikely to be at high risk.

Fracture risk can be affected by factors that may not be included in the risk tool, for example living in a care home or taking drugs that may impair bone metabolism**.** You may also consider assessing risk in patients taking the following medications, particularly in the presence of other risk factors:

- selective serotonin reuptake inhibitors
- antiepileptic medication, particularly enzyme-inducing drugs, such as carbamazepine
- aromatase inhibitors, such as exemastane
- gonadotropin-releasing hormone agonists, such as goserelin
- proton pump inhibitors
- thiazolidinediones, such as pioglitazone
- anti-retroviral drugs

Osteoporosis Treatment Pathway for Adults - Algorithm 1

FRAGILITY FRACTURE ***RISK ASSESSMENT***

Refer to
Fracture Liaison Service (FLS) if available locally

- **Exclude** and **investigate** if secondary / non-osteoporotic causes of fracture suspected
- Osteoporosis **may be assumed** in postmenopausal women > 75 years if DXA unfeasible/inappropriate
- **Consider** DXA scan for patients > 50 years
- **Refer** to specialist premenopausal women and men < 50 years

On or commencing high dose oral corticosteroid **(≥7.5mg prednisolone or equivalent) for ≥ 3 months** – consider treatment

NICE recommend assessment of fracture risk in:

- all women ≥ 65 years and all men ≥75 years
- women under 65 and men under 75 years with any risk factor
- people under 50 years **only** with **major risk factor-in red**

Risk factors include:

- **Previous fragility fracture**
- **Current / frequent use of oral or systemic glucocorticoids**
- History of falls
- Family history of hip fracture
- Other causes of secondary osteoporosis such as:
  - Endocrine diseases including diabetes mellitus, hyperthyroidism, hyperparathyroidism, Cushing's disease, hypogonadism in either sex including **untreated premature menopause** and treatment with aromatase inhibitors or GnRH agonists
  - Malabsorption conditions including IBD, coeliac disease
  - Chronic liver disease
  - Chronic kidney disease
  - Cystic Fibrosis / COPD
  - Rheumatoid arthritis
  - Immobility, e.g. from neurological injury / disease
- Low BMI < 18.5kg/m^2†
- Smoking†
- Alcohol intake >14 units/week for women and men†
- Drug therapy including long term SSRI, anti-epileptics, PPIs and pioglitazone

†Modifiable risks: patients should be encouraged to achieve ideal body weight, stop smoking, reduce alcohol intake, take regular exercise, increase muscle strength and eat a balance diet

1st line treatment options

- **Alendronic acid 70mg once weekly tablets or**
- **Risedronate 35mg once weekly tablets**
- Ensure patient is able to follow administration instructions, (see SPCs) and consider swallowing issues
- Be aware of relevant MHRA safety advice regarding oesophageal reactions, osteonecrosis of jaw and ear and atypical femoral fracture
- If intolerant to initial choice, trial the other
- Seek specialist advice if unsatisfactory response (fracture after 1 yr treatment, decrease in BMD from baseline)

If bisphosphonate is contraindicated or not tolerated, refer for Specialist Management

Calculate 10-year fracture risk using QFracture® or Frax® tool and give lifestyle advice
Consider calcium and vitamin D intake

High Risk | Intermediate Risk | Low Risk

DXA & recalculate fracture risk

High Risk | Low Risk

Lifestyle advice, reassure and reassess in 5 years or less depending on clinical context

2nd line treatment options
If oral bisphosphonate is **contraindicated** or **not tolerated**, consider patient factors:

- For younger patients - referral to secondary care for **zoledronic acid 5mg annual IV infusion** may be preferred OR
- **Denosumab SC injection every 6 months –** lifelong (see prescribing info on PAD)

NICE TA464 *-oral and IV bisphosphonates should be available to people **eligible for risk assessment** and who have been assessed at being at a higher risk of osteoporotic fragility fracture.* **All decisions should be based on what is important to the individual, health priorities, lifestyle and goals – take into account risk of fracture, risk of adverse effects, clinical circumstances and preferences.**

Specialist treatment options-RED status

- **Teriparatide 20mcg daily SC (max duration 18 months, not to be repeated), funding required OR**
- **Strontium ranelate if intolerant to other treatments or they are contraindicated**

ALL patients on **oral bisphosphonates, IV zoledronic acid or denosumab** should receive supplemental calcium and vitamin D daily unless dietary intake of calcium is adequate, (see local preferred products)

Pharmaceutical Management

NICE recommend oral bisphosphonates only if the patient is eligible for risk assessment as defined in NICE CG146 Assessing the risk of fragility fracture. NICE TA 464 Bisphosphonates for treating osteoporosis states that oral and intravenous bisphosphonates are recommended because new analyses show they are cost effective for people who have been assessed as being at higher risk of osteoporotic fragility fracture using the methods recommended in NICE's guideline on osteoporosis and NICE's quality standard on osteoporosis. Algorithm 1 should be followed.

First Line Treatment (local choices) - oral bisphosphonates

Alendronic acid 70mg once weekly* or risedronate 35mg once weekly

*alendronic acid 70mg + colecalciferol 70mcg (Fosavance®) has **non-formulary** status

Generally, bisphosphonates are safe medications if taken correctly. Serious adverse effects are rare and the frequency and severity of the reactions are often dose dependent. (Papapetrou, P., 2009). Rare long-term adverse effects include osteonecrosis of the jaw and ear and atypical femoral fractures-see section **"How long should osteoporosis be treated for?** on page 15.

Concordance is affected when patients experience adverse events, do not understand their condition, do not have enough information about their treatment, do not know about potential side effects and are not reviewed. It can be improved by:

- ensuring patients understand about osteoporosis and their fracture risk
- discussing their treatment options using the NICE patient decision aid
- giving patients detailed information about their treatment including how their medication works, clear administration instructions, any potential side effects and how to minimise them
- encouraging patients to discuss the development of any side effects or problem
- ensuring patients are reviewed 3 – 6 months after starting treatment and regularly thereafter.
- recommending that patients access the resources of The Royal Osteoporosis Society which provides a helpline service run by nurses with specialist knowledge of osteoporosis and bone health and also have local support groups.

Adverse Effects of Bisphosphonates

Adverse Event	Description	Comments
Musculoskeletal Pain	Severe bone, joint and / or muscle pain (which may develop days, months or even years after initiating therapy), (see SPC for further details)	Very common (≥1/10 patients). This can be avoided by monitoring calcium and vitamin D levels before the start of treatment and ensuring adequate levels of these are maintained during treatment
Upper gastrointestinal tract symptoms, severe oesophageal reactions	Nausea, vomiting, epigastric pain, dyspepsia due to mucosal irritation, oesophagitis, oesophageal ulcers, oesophageal strictures, oesophageal erosions (MHRA, Dec 2014)	Common (between ≥1/100 and <1/10). These symptoms are worse if administration instructions are not followed closely
Osteonecrosis of the Jaw (ONJ)	Pain, swelling and infections in the gum, loose teeth, poor healing of gums and numbness or heaviness in the jaw, (MHRA, Nov 2009)	Rare. Risk factors include diabetes, smoking, alcohol use, poor oral hygiene and concurrent use of corticosteroids
Atypical Femoral Fractures	Stress fractures of the proximal femoral shaft can occur after minimal or no trauma in patients on long term therapy, (MHRA, June 2011)	Rare. Patients should be advised to report any thigh, hip or groin pain and then to be evaluated for bilateral incomplete femur fractures
Osteonecrosis of the Ear	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 (MHRA, December 2015)	Rare. Patients should be advised to report any ear pain, discharge from the ear or an ear infection during bisphosphonate treatment

Gastrointestinal Intolerance of bisphosphonates is defined as persistent upper gastrointestinal disturbance which occurs even when the instructions for administration have been followed correctly and is sufficiently severe to warrant discontinuation of treatment. Patients presenting with reflux and dyspepsia should be checked for concordance and their ability to comply with administration instructions discussed.

Bisphosphonates are poorly absorbed orally and absorption is significantly reduced by the presence of food or other medication. They must be taken:

- 30 minutes before the first food and drink (except water) of the day, after not eating overnight
- with 120 - 200mL of plain (not mineral) water
- at least 2 hours before any calcium supplement and 30 minutes before any other medications to achieve an effective dose.

Additionally

- patients must remain upright for 30 minutes after taking the medication and not lie down or return to bed to prevent the bisphosphonate remaining in contact with the mouth or throat for a prolonged period as this can cause ulceration.
- Patients should swallow the bisphosphonate tablet whole; they should not crush or chew the tablet or allow the tablet to dissolve in their mouths because of a potential for oropharyngeal ulceration.
- Use with caution in patients with abnormalities of the oesophagus and other factors which delay oesophageal emptying such as stricture or achalasia (see SPCs)
- In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate on an individual patient basis.

Patients should be advised to report any symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or pain behind the breastbone.
Note: Proton Pump Inhibitors (*PPIs) should **not** be used to treat reflux type symptoms.*

Patients Unable to Swallow Alendronic Acid or Risedronate tablets

The NEWT Guidelines for administration of medication to patients with enteral feeding tubes or swallowing difficulties recommend using alendronic acid 70mg effervescent tablet (Binosto®), or alendronic acid 70mg oral solution. Alternatively consider using once-yearly zoledronic acid.
No information on administering the effervescent tablets or the oral solution via enteral feeding tubes has been located - consult a Pharmacist for further advice.
The effervescent tablets should be taken upon arising for the day dissolved in half a glass of plain water (not less than 120 ml or 4.2 fl.oz.). Dissolving the tablet in water yields a buffered solution of pH 4.8 – 5.4. The buffered solution should be drunk, once the fizzing has subsided and the effervescent tablet has completely dissolved to give a clear to slightly cloudy buffered solution, followed by at least 30 ml (one sixth of a glass) of plain water. Additional plain water may be taken.
Alendronic acid 70mg oral solution should only be swallowed as a single 100 ml dose (i.e. the entire bottle contents) followed by at least 30 ml of plain water; additional plain water may be taken after.
Do not use either preparation in patients who have difficulties swallowing liquids or in whom alendronic acid is contraindicated.

Both formulations have a **GREEN** status on the traffic light system but effervescent tablets are preferred as they are more cost-effective.

Alternative treatments should be discussed with patients unable to comply with the administration directions, i.e. those patients who:

- are unable to stand or sit upright for at least 30 minutes
- have difficulty swallowing tablets or large volumes of liquid
- are at risk of aspiration (solution / liquids cannot be thickened).

Contraindications and Special Precautions for the Use of Bisphosphonates

- alendronic acid and zoledronic acid should be avoided if eGFR < 35mL/min / 1.73 m^2, other bisphosphonates should be avoided if eGFR < 30mL/minute / 1.73m^2 (BNF)
- bisphosphonates should be used with caution in women of childbearing age (BNF)
- bisphosphonates should not be prescribed to premenopausal women; these patients should be referred to a specialist experienced in the treatment of osteoporosis, (CKS)
- a dental examination is recommended prior to treatment and patients should maintain good oral hygiene, have routine dental check-ups and report any oral symptoms (NOGG)
- pre-existing hypocalcaemia must be investigated and treated if appropriate (NOGG).

Unsatisfactory Response

An unsatisfactory response following treatment for secondary prevention of osteoporosis, i.e. after a fragility fracture, is defined as occurring when a patient has another fragility fracture despite adhering fully to treatment for 1 year and there is evidence of a decline in BMD below the pre-treatment baseline. It is recommended that specialist advice should be sought. Where BMD measurement is not possible or appropriate to obtain, NICE suggests that factors known to be indicators of a low BMD such as low body mass index (defined as less than 22 kg/m2), medical conditions (such as ankylosing spondylitis or Crohn's disease), conditions that result in prolonged immobility and untreated premature menopause are used.

Second Line Treatments – Consider the Patient and Practical Implications

- **For younger patients, consider referral to secondary care for IV zoledronic acid annual infusion**
- **For older patients (over 75 years) consider denosumab (Prolia®) 60mg/mL solution for subcutaneous injection every 6 months but should be lifelong**

Following a recent MHRA Safety Alert: Denosumab 60mg (Prolia): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment, it is important to

- Evaluate a patient's individual factors for benefits and risks before initiating treatment with denosumab, particularly in patients at increased risk of vertebral fractures for example those with previous vertebral fracture.
- Counsel patients that they should not stop denosumab treatment without talking to their doctor to discuss their individual risk factors
- Contact a specialist if patient wishes to stop denosumab to discuss alternative options
- Explain to patent that if they miss a prescribed dose of denosumab, the missed injection should be administered as soon as possible. After this, their next injection should be scheduled 6 months from the date of their last injection
- Give patient the reminder card which includes important safety information about osteonecrosis of the jaw and precautions to take
- NICE rapid guidance (30 April 2020) advises not to postpone ongoing treatment with denosumab during the coronavirus (COVID-19) pandemic (see local guidance on PAD)

Locally denosumab has been agreed as a treatment option in primary care for people who have a contraindication to bisphosphonates or who have tried two bisphosphonates in line with NICE TA204.

Primary Prevention: denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who:

- are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments **and**
- who have a combination of T-score, age and number of independent clinical risk factors for fracture (history of hip fracture, alcohol intake of more than 14 units per week and rheumatoid arthritis). See NICE TA204 for full information.

Secondary Prevention: denosumab is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.

The recommended dose of denosumab is 60mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or back of the arm. Patients must be adequately supplemented with calcium and vitamin D. It is important to identify patients at risk for hypocalcaemia and this must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during

treatment calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.

For further information see Prescribing Information Sheet on the PAD.

Contraindications and Special Precautions for the Use of Denosumab

Certain patients should remain under the care of the secondary care clinicians, i.e.:

- renal patients with Chronic Kidney Disease (CKD) stage 4 or 5
- patients with a T-score of <-4.5.

Adverse Effects of Denosumab

Adverse Event	Description	Comments
Atypical fractures of the femur	Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur (MHRA, Feb 2013)	Patients should be advised to report new or unusual thigh, hip or groin pain
Osteonecrosis of the Jaw (ONJ)	Pain, swelling and infections in the gum, loose teeth, poor healing of gums and numbness or heaviness in the jaw, (MHRA, Sept 2014)	Rare. Risk factors include smoking, age, poor oral hygiene, invasive dental procedures, advanced cancer, previous bisphosphonate treatment and concurrent use of chemotherapy, corticosteroids, angiogenesis inhibitors, radiotherapy to head and neck. Doctors should evaluate all patients for ONJ risk factors prior to treatment. A dental examination with appropriate preventive dentistry is recommended in patients with concomitant risk factors. Patients should be encouraged to maintain good oral hygiene practices, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain, or swelling during treatment. Access patient reminder card here
Osteonecrosis of the external auditory canal	The possibility of osteonecrosis of the external auditory canal should be considered in patients who present with ear symptoms including chronic ear infections or in those with suspected cholesteatoma (MHRA, June 2017)	Patients should be advised to report any ear pain, discharge from the ear or an ear infection
Hypocalcaemia	Muscle spasms, twitches, cramps and numbness in fingers, toes, or mouth, MHRA, Sept 2014)	Patients should have their calcium levels checked before the first dose and two weeks later in patients pre-disposed to hypocalcaemia and subsequently before every dose
Infections	Urinary tract infections, upper respiratory tract infections, diverticulitis, cellulitis, ear infections (Prolia® SPC)	Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis
Increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment	An increased risk of multiple vertebral fractures has been reported in patients within 18 months of stopping or delaying ongoing denosumab 60mg treatment for osteoporosis. Patients with a previous vertebral fracture may be at highest risk. Patients should not stop denosumab without specialist review. (MHRA, August 2020).	Evaluate a patient's individual factors for benefits and risks before initiating treatment with denosumab 60mg, particularly in those with previous vertebral fracture. Patients should not stop denosumab treatment without talking to their doctor to discuss their individual risk factors. If a prescribed dose of denosumab is missed, the missed injection should be administered as soon as possible. After this, schedule the next injection for 6 months from the date of the last injection

Rare Adverse Effects of Bisphosphonates and Denosumab

- **Osteonecrosis of the jaw** occurs only very rarely in patients receiving bisphosphonate or denosumab therapy for osteoporosis. Risk factors for osteonecrosis of the jaw include poor oral hygiene, dental disease, dental interventions, cancer, chemotherapy or glucocorticoid therapy. The incidence of osteonecrosis of the jaw is substantially greater with the higher doses of bisphosphonates or denosumab that are used to treat patients with skeletal metastases.
- **Atypical femoral fractures**, mainly of the subtrochanteric and diaphyseal regions of the femoral shaft, have been reported rarely in patients taking bisphosphonates and denosumab for osteoporosis. Atypical femoral fractures are often bilateral, associated with prodromal pain and tend to heal poorly. During bisphosphonate or denosumab therapy patients should be advised to report any unexplained thigh, groin or hip pain and if such symptoms develop, imaging of the femur (X-ray, isotope scanning or MRI) should be performed. If an atypical fracture is present, the contralateral femur should also be imaged. Discontinuation of bisphosphonate or denosumab therapy should be considered in patients who develop an atypical fracture, weight-bearing activity should be restricted and alternative treatment options considered where appropriate. Surgical treatment with intramedullary nailing is often recommended.

Specialist Treatments

Treatment options that must be initiated and maintained in secondary care include zoledronic acid, strontium and teriparatide†

Intravenous zoledronic acid may be considered for patients if they have difficulty taking oral bisphosphonates or these drugs are contraindicated or not tolerated. It may be more appropriate for younger patients than denosumab

† in line with NICE guidance, funding required

Strontium

Strontium ranelate (Protelos®) 2g granules for oral suspension was voluntarily withdrawn from the market by Servier in August 2017 however, Strontium ranelate Aristo 2g granules for oral suspension was introduced in April 2018.

It is only licensed for the treatment of severe osteoporosis in postmenopausal women and adult men at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. The decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risks.

Treatment should only be initiated by a physician with experience in the treatment of osteoporosis and locally it has a **RED** status.

Educational risk minimisation materials are available online including a Patient Alert Card and Prescriber Guide and Checklist. The decision to initiate strontium ranelate should be based on an assessment of the individual patient's overall risk. The patient should be fully informed of these risks and treatment should be re-evaluated every 6 to 12 months especially with regards to any changes in the patient's cardiovascular risks.

Strontium ranelate should not be used in patients with:

- Current or previous ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Uncontrolled hypertension.
- Current or previous Venous Thromboembolic Events (VTE), including deep vein thrombosis
  and pulmonary embolism.
- Temporary or permanent immobilisation (e.g. post-surgical recovery or prolonged bed rest).
- Hypersensitivity to strontium ranelate or to any of the excipients.

For full warnings and recommendations see SPC.

How Long should Osteoporosis be Treated For?

Concerns over rare adverse effects of long-term bisphosphonate therapy, particularly osteonecrosis of the jaw and atypical femoral fractures, have raised questions about the optimal duration of therapy. Because bisphosphonates are retained in bone for varying periods of time, beneficial effects may persist for some time after cessation of treatment.

CKS recommends that the need for continued treatment should be reviewed every 3-5 years and NICE NG56, Sept 2016, Multimorbidity: clinical assessment and management, recommends discussing stopping bisphosphonate after 3 years and including:

- patient choice
- fracture risk
- and life expectancy in the discussion.

It is also important to consider co-morbidities and polypharmacy as well as the ability of the patient to comply with administration instructions.

For patients who remain at high risk of an osteoporotic fragility fracture:

Includes patients who are:

- aged over 75 years,
- have a previous hip or vertebral fracture
- occurrence of one or more low trauma fractures during treatment, after exclusion of poor adherence to treatment (for example less than 80% of treatment has been taken) and after causes of secondary osteoporosis have been excluded
- current treatment with oral corticosteroids ≥7.5 mg prednisolone/day or equivalent

Continue treatment with oral bisphosphonate for up to 10 years (in total). There is no evidence base to guide decisions about treatment beyond 10 years and management of such patients should be considered on an individual basis. Remind patient there is no consistent evidence that **carrying on treatment** for more than 3 years will protect against breaking a bone nor that there are **harms from stopping** treatment after 3 years (NICE decision support tool)

For other patients:

- arrange a DXA scan (if available and appropriate) and consider:
  - continuing treatment if the T-score < -2.5, reassessing their fracture risk and BMD every 3-5 years
  - stopping treatment if the BMD T-score > -2.5, reassessing their fracture risk and re-measuring BMD after 2 years.

For patients who sustain a fracture whilst taking bone-sparing therapy

- Check concordance
- Exclude secondary causes of osteoporosis
- Re-evaluate treatment choice and consider referral to a specialist for advice on drug treatment
- Continue treatment to reduce the risk of further fractures

For patients taking oral or systemic glucocorticoids:

- Continue treatment with bisphosphonate and/ or calcium and vitamin D, and reassess with FRAX/NOGG every 3-5 years as some patients may be advised to have treatment breaks (prolonged bisphosphonate usage, low prednisolone dose)
- when the glucocorticoid treatment is stopped reassess the osteoporotic fragility fracture risk to determine the need for continuing treatment with a bisphosphonate and / or calcium and vitamin D supplement.

There is no evidence base to guide decisions beyond 10 years of treatment and management options in such patients should be considered on an individual basis (NOGG) and specialist advice should be sought

For patients prescribed zoledronic acid:

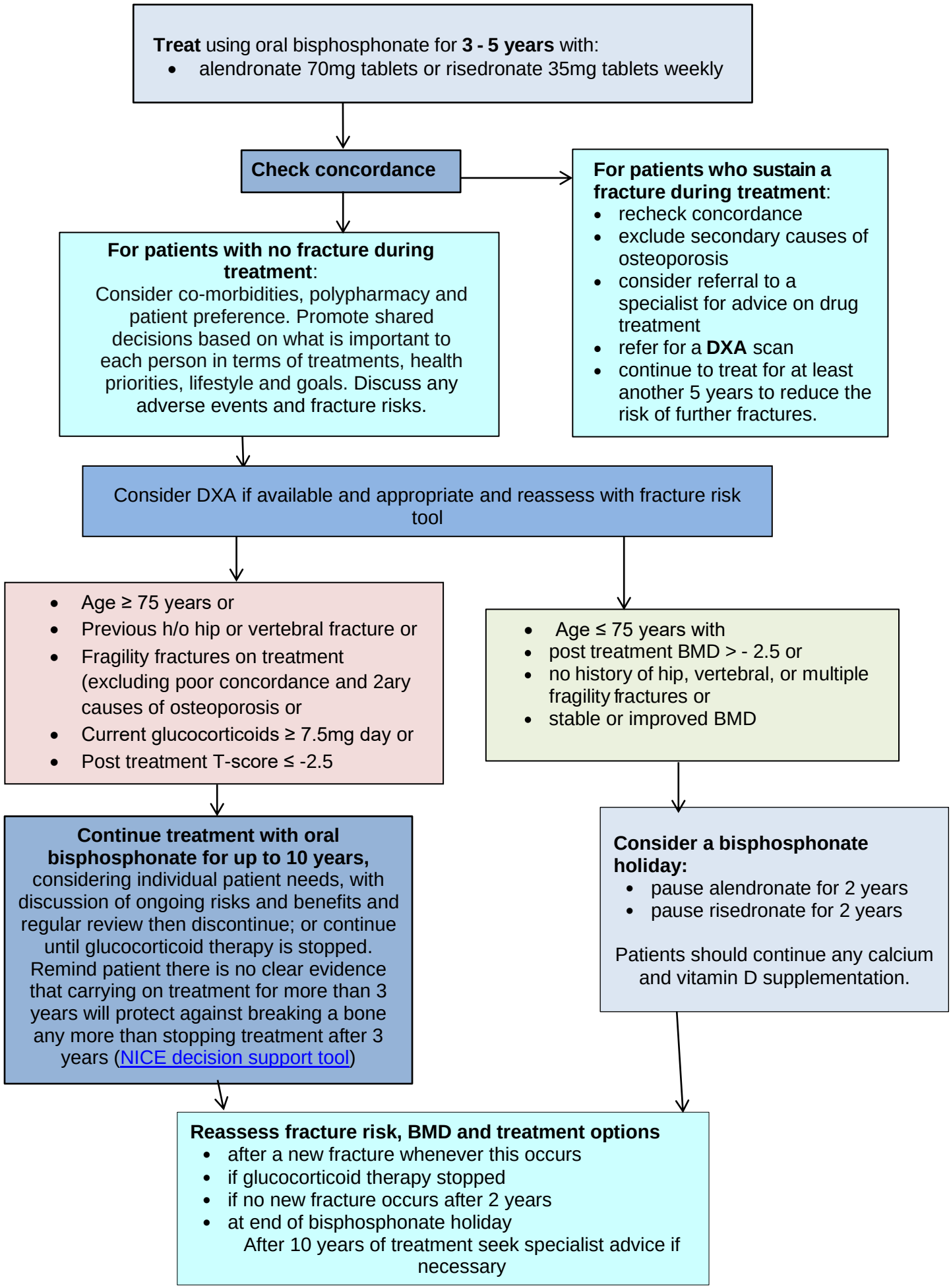
- the beneficial effects of zoledronic acid after three years of treatment continue for another three years once the therapy is stopped
- pause treatment after 3 years and review the case for continued therapy 3 years later
- there may be an increased risk of vertebral fracture if treatment is stopped in patients with a previous vertebral fracture or a pre-treatment hip BMD T-score ≤ -2.5 SD.

For patients prescribed other anti-osteoporotic treatments, (e.g. denosumab):

- The optimal duration of denosumab treatment for osteoporosis has not been established; re-evaluate the need for continued treatment periodically based on the expected benefits and potential risks of denosumab on an individual patient basis, particularly after 5 or more years of use
- An increased risk of multiple vertebral fractures has been reported in patients within 18 months of stopping or delaying ongoing denosumab 60mg treatment for osteoporosis;
- Review patient to ensure concordance with treatment.
- (NB. teriparatide is not included here as treatment is for 18 months only).

If a patient has a new fracture during their treatment break, they should be reassessed immediately.

Review of Long-Term Bisphosphonate Therapy in Primary Care - Algorithm 2



Osteoporosis in Men

Treatments have been less extensively evaluated in men with osteoporosis than in women, though there is no evidence that skeletal metabolism differs fundamentally from that of women, (NOGG).

Alendronate*, risedronate*, zoledronic acid, denosumab and teriparatide† are licensed for the treatment of osteoporosis in men.

Alendronate and risedronate should be the first line treatments in the majority of cases.

*Only alendronate 10mg daily tablet and risedronate 35mg weekly tablet are licensed for use in men.
† This is not routinely funded by NHSE, may apply for funding by IFR.

- In men who are intolerant of oral bisphosphonates or in whom they are contraindicated, zoledronic acid, denosumab and teriparatide are alternative options.
- For the purposes of FRAX calculations, the BMD T-scores in men are calculated based on the female reference database.
- Secondary causes of osteoporosis are commonly found amongst men.
- Intervention thresholds for men are similar to those recommended for women.
- Consideration should be given to referring men with osteoporosis to specialist management, particularly younger men or those with severe disease.

Androgen Deprivation Therapy

All men starting on androgen deprivation therapy:

- should have their fracture risk assessed, NICE clinical guideline 146
- should **not** be routinely offered bone-protective therapy to prevent osteoporosis
- should be offered bisphosphonates if they already have a diagnosis of osteoporosis
- should consider denosumab if bisphosphonates are contraindicated or not tolerated

Glucocorticoid-induced Osteoporosis - NOGG Guidance

Bone loss and an increased fracture risk occur rapidly after initiation of glucocorticoid therapy and increase with the dose and duration of therapy. The increase in fracture risk is seen for vertebral and non-vertebral fractures, including hip fractures, and is partially independent of BMD.

To reduce the risk of osteoporosis, doses of oral corticosteroids should be as low as possible and courses of treatment should be as short as possible. The risk of osteoporosis may be related to the cumulative dose of glucocorticoids; intermittent courses can therefore increase the risk as well as the long-term use of high-dose inhaled corticosteroids. However, the evidence on inhaled glucocorticoids is inconsistent and it is not possible to form a recommendation

- All patients taking high doses of oral glucocorticoids (≥7.5 mg/day prednisolone or equivalent), for more than 3 months should be considered for bone protective therapy.
- In other individuals fracture probability should be assessed.
- Bone-protective treatment should be started at the onset of glucocorticoid therapy in individuals at high risk of fracture.
- Alendronate and risedronate are first line treatment options (caution in patients under 40 and pre-menopausal women / women of childbearing age; referral of these cases to secondary care is recommended). Where these are contraindicated or not tolerated, zoledronic acid or teriparatide are alternative options through specialist management only.
- Patients on glucocorticoid should be re-evaluated every 3-5 years using FRAX/NOGG to decide whether a treatment break from bisphosphonate is advised.

Aromatase Inhibitors and Osteoporosis

Aromatase inhibitors reduce oestrogen levels which increases the rate of bone turnover and can cause significant and very rapid bone density loss of up to 8% per year in younger women.

NICE guidance (NICE NG101) is to offer a baseline dual-energy X-ray absorptiometry (DEXA) scan to assess bone mineral density (BMD) in women with invasive breast cancer who are not receiving bisphosphonates as adjuvant therapy and who:

- are starting adjuvant aromatase inhibitor treatment or
- have treatment-induced menopause or
- are starting ovarian ablation / suppression therapy, (NICE NG101).

Do not offer a DEXA scan to patients with early invasive breast cancer who are receiving tamoxifen alone, regardless of pre-treatment menopausal status.

Offer bisphosphonates to postmenopausal women treated with an aromatase inhibitor if T-score is < -2. For women with premature menopause requiring treatment with an aromatase inhibitor please refer to the 'Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK expert group' (2008)

Lifestyle and Dietary Measures

- A daily calcium intake of between 700 and 1200mg should be advised, this should be achieved through dietary intake if possible, with use of supplements only if necessary. In postmenopausal women and older men receiving bone protective therapy for osteoporosis, calcium supplementation should be given if the dietary intake is below 700mg / day and vitamin D supplementation considered in those at risk of, or with evidence of, vitamin D insufficiency.
- It is appropriate to test vitamin D levels in patients prior to starting anti-resorptive therapy (see Vitamin D Pathway in Patients with Bone Disease on PAD).
- The Royal Osteoporosis Society recommend that people with osteoporosis should take a vitamin D supplement all year round of at least 400 IU (10microgram) in line with national guidance and produce a useful leaflet on Vitamin D supplements and tests.
- NOGG recommend that in postmenopausal women and men ≥50 years who are at increased risk of fracture, a daily dose of 800 IU of vitamin D should be advised
- However, **all** patients on **oral bisphosphonates, iv zoledronic acid or denosumab** should receive supplemental calcium and vitamin D daily unless dietary intake of calcium is adequate
- Regular weight-bearing exercise should be advised, tailored according to the needs and abilities of the individual patient.
- A falls history should be obtained from patients at increased risk of fracture and a further assessment and appropriate measures undertaken in those at risk.

Advice to Patients

Patients should be:

- encouraged to take an adequate calcium intake (700mg / day) throughout their life; calcium-rich foods include milk, dairy products and vegetables e.g. broccoli
- encouraged to estimate their dietary calcium intake using an online calculator and the BDA Food Fact Sheet Calcium
- advised to take 10 micrograms (400 international units) of vitamin D in line with national guidance if their calcium intake is adequate. Give BDA Food Fact Sheet Vitamin D or ROS leaflet Vitamin D supplements and tests.
- prescribed a calcium and vitamin D supplement in line with local guidance, (see Appendix 1), if calcium intake is inadequate.

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With acknowledgement to Derbyshire Joint Area Prescribing Committee for Algorithm 1 & 2

Appendix 1: Local preferred calcium and vitamin D products

Generic Description	Available Brand(s)	Dose	Cost for 28 days	Flavour	Suitable for vegetarians/vegans?	Comments
Calcium carbonate 1.5g (equivalent to calcium 600mg) / vitamin D3 400iu tablets	Accrete D3 tablets	One twice a day	£2.75	n/a	Contains gelatin: unsuitable for vegetarians and vegans. Not Halal or Kosher certified. Contains soya bean oil.	Large tablet but scored so can be broken in half, but this may be difficult and tablets are not chewable
Calcium carbonate 750mg (equivalent to calcium 300mg) / vitamin D3 200iu tablets	Adcal D3 caplets	Two twice a day	£2.95	n/a	Free of ingredients of animal origin but vitamin D derived from the lanolin of sheep's wool. Manufacturer states they may be suitable for vegetarians but not vegans. No soya bean oil-suitable if peanut or soya allergy.	AdcalConnect reminder service
Calcium carbonate 1.5g (equivalent to calcium 600mg) / vitamin D3 400iu chewable tablets	Adcal D3 chewable tablets	One twice a day	£3.65	fruit or lemon	Contains gelatin: unsuitable for vegetarians and vegans. Not Halal or Kosher certified. Contains soya bean oil.	Chewable tabs may not be palatable for some patients. AdcalConnect reminder service NB other branded generics are available so excipients may differ
Calcium carbonate 1.5g (equivalent to calcium 600mg) / vitamin D3 400iu effervescent	Adcal D3 Dissolve tablets	One twice a day in water	£5.99	lemon	Contains gelatin: unsuitable for vegetarians and vegans	Should be reserved for patients requiring soluble preparation. AdcalConnect reminder service
Calcium carbonate 2.5g (equivalent to calcium 1000mg) / vitamin D3 880iu chewable tablets	Accrete D3 chewable tablets	One daily	£2.75	orange	Does not contain gelatin or soya; halal and kosher “friendly”	Can improve compliance as once daily and reduces pill burden. May be divided in half.
Calcium carbonate 2.5g (equivalent to calcium 1000mg) / vitamin D3 1000iu chewable tablets	Calci-D tablets	One daily	£2.25	fruit	Does not contain gelatin or soya	Can improve compliance as once daily and reduces pill burden
Calcium carbonate 2.5g (equivalent to calcium 1000mg) / vitamin D3 800iu chewable tablets	TheiCal D3 1000mg/880 unit chewable tablets	One daily	£2.75	orange	Does not contain gelatin, suitable for vegetarians but not vegans. No nut or peanut oil.	Can improve compliance as once daily, disintegrates in the mouth and reduces pill burden

Please note that information on Halal and Kosher status is supplied by the manufacturer and does not guarantee that these products are suitable for all patients with these dietary requirements who are advised to contact the manufacturer for full information. Prices from MIMS December 2020.