3T's Primary & Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women

For cases that fall outside of this guidance, such as men, pre-menopausal women, osteopaenia etc. specialist referral may be necessary but also the NOGG guidance referred to below may be of use.

Assessing fracture risk with the FRAX (Fracture Risk Assessment) tool:
www.shef.ac.uk/FRAX/

It is recommended that the FRAX tool is used to assess all patients that are >40 yrs of age and **who have not had ANY drug treatment for osteoporosis previously** (except calcium/vitamin D supplements). This can be used to help decide where the intervention threshold for treatment lies but is not a substitute for clinical judgement.
The **FRAX tool** was developed by the World Health Organisation to evaluate fracture risk in individual patients, integrating clinical risk factors and bone mineral density (BMD) at the femoral neck.
It gives you the10-year probability of a hip and major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).
It can be used for both women & men. It will under estimate risk in patients aged >75 yrs of age.

- The **National Osteoporosis Guideline Group (NOGG)** have produced a guideline for the diagnosis and management of osteoporosis which covers postmenopausal women & men from the age of 50 years in the UK. This can be used in collaboration with FRAX and their guidance can be found at: **www.shef.ac.uk/NOGG/**
- The **South West Osteoporosis Interest Group (SWOIG)** guidance entitled "Implementation of recent guidelines relating to osteoporosis" may also be referred to.

When are Drug Treatments recommended?

PRIMARY PREVENTION (as per NICE TA160):

Women aged 70 yrs or older: - Who have an independent clinical risk factor (see below) for fracture OR an indicator of low BMD (see below) AND who have confirmed osteoporosis (T-score of -2.5 SD or below). In women aged 75 yrs and above who have two or more independent clinical risk factors for fracture or indicators of low BMD, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.
Women aged 60-69 years: Who have an independent clinical risk factor (see below) for fracture & who are confirmed to have osteoporosis (that is, a T-score of -2.5 SD or below).
Postmenopausal women younger than 65 years: Who have an independent clinical risk factor (see below) for fracture and at least one additional indicator of low BMD & who are confirmed to have osteoporosis (T-score of -2.5 SD or below).

SECONDARY PREVENTION

Women who are **confirmed to have osteoporosis** (that is, a T-score of -2.5 SD or below) and have sustained a clinically apparent osteoporotic fragility fracture. For women aged **75 years or older, there is no need for prior DEXA** scanning if the clinician considers this is clinically inappropriate or unfeasible (as per NICE TA 161).
For women who have had **2+ vertebral fractures**, treatment may be started while waiting for a DEXA scan (as per The National Orthopaedic Guideline Group (NOGG).
NOGG recommend that "women with a prior fragility fracture should be considered for treatment without the need for further risk assessment, although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women." www.shef.ac.uk/NOGG/.
This may result in more women receiving treatment than what NICE guidelines recommend & each case should be considered using all assessment models available and a decision reached between patient and clinician.

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Independent clinical risk factors:
- Parental history of hip fracture
- Alcohol intake ≥4 units/day
- Rheumatoid arthritis

Indicators of low bone mass density (BMD):

Low body mass index (less than 22kg/m^2)	Ankylosing spondylitis
Crohn's disease	Hyperparathyroidism
Prolonged secondary amenorrhea	Anorexia nervosa
Malabsorption	Coeliac Disease
Conditions that result in prolonged immobility	Untreated menopause

Prescribe all patients calcium & vitamin D supplements unless the clinician is confident that the patient has adequate calcium intake & is vitamin D replete:

Check calcium levels. Any patients with hypocalcaemia or at risk of low serum calcium should be started on the calcium & vitamin D supplement as below. Serum calcium levels should be corrected before starting any osteoporosis medication:
Calcium 1g + Vitamin D 800iu (preferred brand is Calceos).

Vitamin D Deficiency

Some patients are more at risk of vitamin D deficiency including the elderly, frail and housebound, patients with malabsorption and hypocalcaemia and patients taking anti epileptic medication. For these patients it would be advisable to measure the patient's vitamin D levels. Any vitamin D deficiency found should be corrected following advice from a consultant.

Avoid cholecalciferol in severe renal impairment as it cannot be converted to its active form in the renally impaired. Seek specialist advice in such cases.

Patients should also be counselled about lifestyle measures:

Weight bearing exercise	Stop smoking
Reduce risk of falls	Reduce alcohol intake

Maximise calcium & vitamin D intake plus supplements

SPECIALIST REFERRAL IS RECOMMENDED IN THE FOLLOWING SITUATIONS

Continued bone loss or fracture despite treatment
Drug intolerance if advice required

Formulary status of drugs.

Alendronate, Risedronate (2nd line) and **Strontium** are all GREEN drugs in the formularies used by health care professionals in Wiltshire (3T's (GWH), BCAP (RUH) and ICID (SDH).
Raloxifene is a GREEN drug (2nd line) on 3Ts and ICID. It is not currently on the BCAP formulary which is being addressed.
Denosumab is an AMBER drug and requires initiation by a consultant followed by continuation by the GP.
Zolendronic acid and **Teriparatide** are **RED** drugs on all formularies used in Wiltshire and are **secondary care only** drugs.

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Renal impairment

Bisphosphonates should be **avoided** in patients with moderate to severe renal impairment (calculated creatinine clearance:
< 35ml / minute for alendronate
< 30ml / minute for risedronate)

Strontium Ranelate should be avoided in patients with moderate to severe renal impairment. (calculated creatinine clearance < 30ml / minute)

No dose adjustment of **Denosumab** is necessary in renal impairment and therefore may offer an alternative for patients with renal impairment.

Local variations

It should be noted that the three local hospitals used by the majority of NHS Wiltshire patients may differ in how often they review patients on Denosumab & how often they call the patients for DEXA scans. Please contact your local specialist team for advice on their specific arrangements.

It should also be noted that this guidance represents the pathway for the majority of patients and that some consultants may wish to deviate from this in certain circumstances.

Duration of treatment

Current evidence suggests 5 years of treatment (except Teriparatide which is licensed to be used for up to 18 months). However, for patients on Zolendronic acid, current evidence suggests that 3 years may be the optimum duration of treatment. As this drug is secondary care only, the consultant looking after the patient will decide on treatment duration.
Those patients not otherwise at increased risk of vertebral fracture may then consider a "holiday period" of up to 5 years without therapy, but patients with vertebral fractures should continue treatment indefinitely. Women at very high risk of fragility fractures may benefit by continuing beyond 5 years treatment, seek specialist advice in such cases.

Action:

- Assess at 5 years with a repeat DXA (but seek advice if pt is on Strontium). If BMD stable or higher than base line have a 5 year drug holiday re-assessing only if there is sudden height loss or a new fracture.
- If BMD is lower than base-line seek specialist advice. The specialist may decide to continue treatment or change therapy.

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Treatment pathway for PRIMARY PREVENTION of osteoporosis in postmenopausal women.

1st line: ORAL BISPHOSPHONATES

Please note that if a patient has minor side-effects with one generic version of alendronate it is worth trying a different generic version as the patient may tolerate it better.

First-line oral bisphosphonate: Alendronic acid 70mg po each week.

Unable to comply with administration

Try Denosumab- see below.

Contraindication

- Abnormality of the oesophagus & other factors which delay emptying (e.g. stricture or achlasia)- **Try Risedronate -see below.**

- Hypocalcaemia –Treat hypocalcaemia first or seek specialist advice if necessary.

Intolerance

Persistent upper GI disturbance that is sufficiently severe to warrant discontinuation of treatment & that occurs even though administration instructions were followed. **Try Risedronate- see below.**

Second-line oral bisphosphonate: Risedronate 35mg po each week.

Contraindication

Hypocalcaemia- Treat hypocalcaemia first or seek specialist advice if necessary.

Intolerance

Persistent upper GI disturbance that is sufficiently severe to warrant discontinuation of treatment & that occurs even though administration instructions were followed. **Move to 2nd line options, Strontium or Denosumab.**

2nd line:

OR

Strontium 2g po nocte. *N.B. May affect validity of future scans.*

If pt unable to comply with administration requirements,

Contra-indication: Hypersensitivity

Intolerance: Persistent nausea or diarrhoea, either of which warrants discontinuation of treatment.

Try Denosumab.

Denosumab 60mg s.c. every 6 months.
Consultant initiation ONLY

Contraindications: Hypocalcaemia or Hypersensitivity

Intolerance: Seek specialist advice

N.B. Hip fracture reduction evidence for Strontium is only in sub-sets of patients over the age of 75 (post-hoc analysis).
Strontium "falsely" increases bone density, up to 50%, hence BMD reading subsequently not reliable.

If none of the above options are suitable for your patient, then a referral to a specialist is recommended for alternative treatments.

Treatment pathway for SECONDARY PREVENTION of osteoporosis in postmenopausal women.

1st line: ORAL BISPHOSPHONATES

Please note that if a patient has minor side-effects with one generic version of alendronate it is worth trying a different generic version as the patient may tolerate it better.

First-line oral bisphosphonate: Alendronic acid 70mg po each week.

Unable to comply with administration

Try 2nd line options, Denosumab or Raloxifene if suitable.

Contraindication

Abnormality of the oesophagus & other factors which delay emptying (e.g. stricture or achlasia)- **Try Risedronate -see below.**

Hypocalcaemia – Treat hypocalcaemia first or seek specialist advice if necessary.

Intolerance

Persistent upper GI disturbance that is sufficiently severe to warrant discontinuation of treatment & that occurs even though administration instructions were followed.

Try Risedronate.

Unsatisfactory response

Another fragility fracture despite adhering to treatment for one year **AND** there is evidence of a decline in BMD below her pre treatment baseline (from NICE TA161):

N.B. If the FRAX tool indicated treatment without a baseline DEXA, request a DEXA & if osteoporosis and osteopaenia are seen:

Move to 2nd line option.

Second-line oral bisphosphonate: Risedronate 35mg po each week.

Unsatisfactory response

Contraindication

Hypocalcaemia
Treat hypocalcaemia first or seek specialist advice if necessary.

Intolerance

Persistant upper GI disturbance that is sufficiently severe to warrant discontinuation of treatment & that occurs even though administration instructions were followed. **Move to 2nd line option.**

2nd line options:

Strontium 2g po nocte.
N.B. May affect validity of future scans- see below.

If patient unable to comply with administration requirements

Contra-indication: Hypersensitivity

Intolerance: Persistent nausea or diarrhoea, either of which warrants discontinuation of treatment.

Try Denosumab or Raloxifene if suitable.

N.B. Hip fracture reduction evidence only in sub-sets of patients (post-hoc analysis).
"Falsely" increases bone density, up to 50%, hence BMD reading subsequently not reliable.

Raloxifene 60mg po OD
N.B. Not adequately evaluated in non-vertebral & hip fracture

Contraindications: Hypersensitivity to active substance or any excipients. Must not be used in women with child bearing potential. Active or past history of venous thromboembolic events (VTE), Hepatic impairment including cholestasis. Severe renal impairment. Unexplained uterine bleeding. Patients with signs or symptoms of endometrial cancer

Try other 2nd line options if suitable, otherwise specialist referral required.

Denosumab 60mg s.c. every 6 months.
Consultant initiation only

Contraindications: Hypocalcaemia or Hypersensitivity

Intolerance: Seek specialist advice

Unsatisfactory response: When a woman has another fragility fracture despite adhering to treatment for one year AND there is evidence of a decline in bone mass density below her pre treatment baseline.

Move to 3rd line option- referral to specialist required.

Prepared by: Rachel Hobson, NHS Wiltshire Formulary Pharmacist.

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SECONDARY PREVENTION (cont)

3rd Line

Zolendronic Acid 5mg IV infusion annually. *Secondary care only*

Contra-indications: Women of child-bearing potential, Hypocalcaemia, Pregnancy & breastfeeding Hypersensitivity.

Unsatisfactory Response: When a woman has another fragility fracture despite adhering to treatment for one year AND there is evidence of a decline in bone mass density below her pre treatment baseline.

Move to 4th line option

4th Line

Teriparatide 20mcg OD by sc injection. *Secondary Care only* Max duration of treatment 18 months.

Consider early referral for Teriparatide in severe vertebral (or glucocorticoid induced osteoporosis) not responding to conventional treatment.

Contra-indications: Pre-existing hypercalcaemia, Skeletal malignancies or bone metastases, Metabolic bone diseases inc. Paget's & hyperparathyroidism, Unexplained raised alkaline phosphatase; Previous radiation therapy to the skeleton.

Unsatisfactory Response:
When a woman has another fragility fracture despite adhering to treatment for one year AND there is evidence of a decline in bone mass density below her pre treatment baseline.

Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women: who are unable to take alendronate and either risedronate or etidronate, or have a contraindication to or are intolerant of alendronate and either risedronate or etidronate, **or** who have a contraindication to, or are intolerant of strontium ranelate, **or** who have had an unsatisfactory response to treatment with alendronate, risedronate or etidronate **and** who are 65 years or older and have a T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, **or** who are aged 55–64 years and have a T-score of –4 SD or below plus more than two fractures. (from NICE TA161)

References:

- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. NICE TA160 October 2008http://guidance.nice.org.uk/TA160
- Denosumab for the prevention of osteoporotic fractures in postmenopausal women. NICE TA 204 October 2010. http://www.nice.org.uk/nicemedia/live/13251/51293/51293.pdf
- Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. NICE TA161 October 2008 http://www.nice.org.uk/TA161

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