OSTEOPOROSIS -Medical Management of Men and Women who have (or are at risk of) Osteoporosis

Risk Factors

Current or frequent past use of glucocorticoids

→ **Refer to separate guidance on page 3 of guidelines**

No

Previous fragility fracture (including vertebral fractures)

Yes → **Refer to separate guidance on page 2 of guidelines**

No

Use Frax® assessment tool to assess fracture risk
(see page 5 of guidelines)

http://www.shef.ac.uk/FRAX
then
use the link to NOGG guidance

Measure BMD if recommended and recalculate fracture risk

Reassure, **General measures[2],** **Reassess in ≤ 5 yrs depending on clinical context**	**Investigate[1]** **and** **Advise treatment**

Frail, increased fall risk + housebound

→ **Advise calcium 1 – 1.2 gram and colecalciferol 20 micrograms (800 units) daily**

Assess falls risk. Advise or refer to Falls Service as appropriate

Advise Treatment
ALENDRONATE 70mg WEEKLY (*1st Line*)

Advise three/six monthly review of adherence to therapy as non-compliance is common.
Seek specialist opinion if patient sustains a fracture after 1 year on compliant therapy.

Consider any of the following 2nd line treatments if alendronate not suitable because patient

- **unable to comply with the special instructions for the administration of alendronate**
- **has a contraindication to, is intolerant of, or has a lack of clinical response to alendronate**

ALTERNATIVE BISPHOSPHONATE (Including intravenous bisphosphonates)	DENOSUMAB 60mg s.c. injection Administered every 6 months	RALOXIFENE 60mg daily	STRONTIUM 2 g at night
Refer to Page 6 and Table A on Page 10 of guidelines	Green Drug see GP Information Sheet* Refer to page 7 of guidelines	Refer to page 8 of guidelines	Restricted indications only Refer to page 8 of guidelines

Specialist Initiated **Teriparatide (refer to page 8 of guidelines)**

All patients must be prescribed
Calcium 1 – 1.2 gram + colecalciferol 20 micrograms (800 units) daily
unless clinician is confident dietary calcium intake is adequate (approx. 1gram per day) and patient is vitamin D replete. (see link to dietary calcium calculator)[15]. Prescribe vitamin D 800 units daily alone in patients with adequate calcium intake who only need vitamin D supplement.

* Please consult the GP Information Sheet [16] at West Hampshire CCG website

[1]Investigations

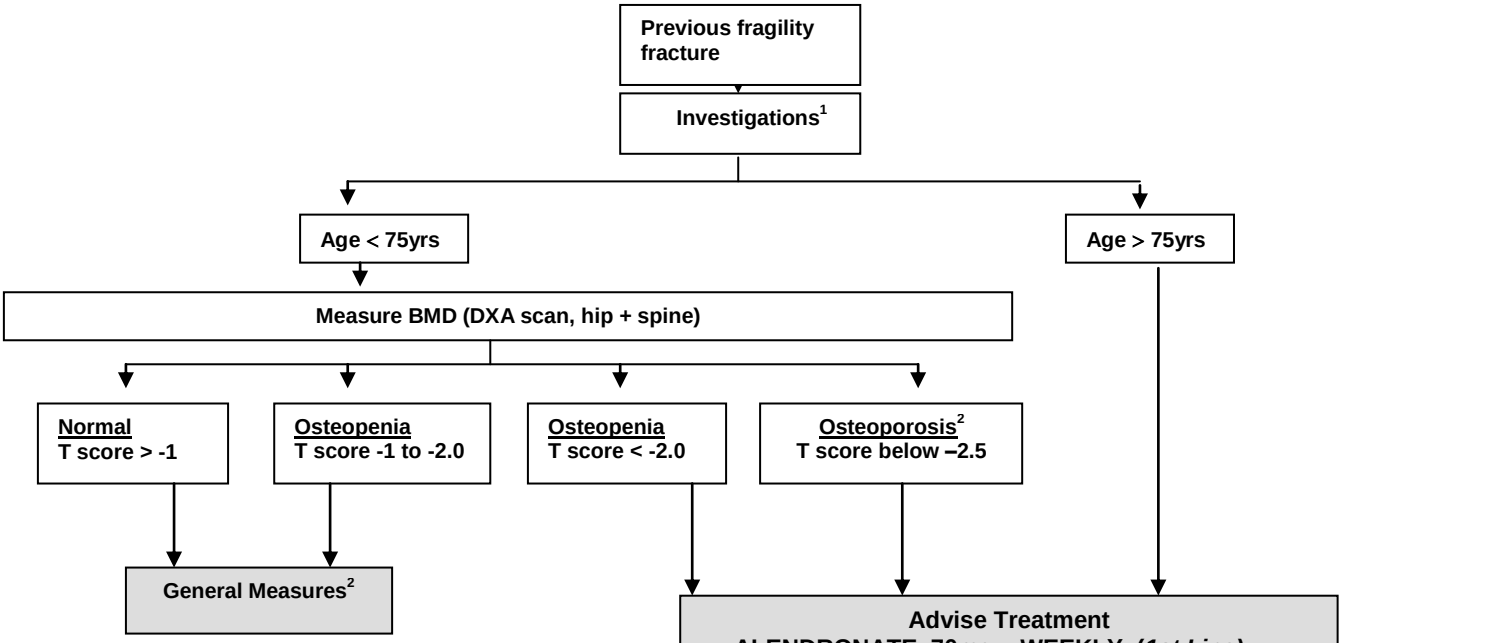
- FBC, ESR (If ESR raised, measure serum paraproteins and urine Bence Jones protein)
- Bone and liver function tests (Ca, P, Alk phos, albumin, ALT)
- Renal function
- Serum 25 0H Vit D
  Consider PTH if:
  - Calcium level raised
  - Calcium level in upper quartile of normal range and vitamin D deficient

  Additional tests if indicated:
- Serum TSH
- Coeliac screen (TTG)
- Serum testosterone, LH and SHBG, PSA (men)
- Consider γGT
- Lateral thoracic and lumbar spine X rays
- BMD if monitoring required
- Consider Isotope bone scan

[2]General measures

- Recommend good nutrition esp. with adequate calcium and vitamin D (see link to dietary calcium calculator)[15]
- Recommend regular weight bearing exercise
- Maintain ideal body weight
- Avoid tobacco use and alcohol abuse
  Assess falls risk and give advice if appropriate

ALGORITHM FOR THE MEDICAL MANAGEMENT OF ADULTS WITH PREVIOUS FRAGILITY FRACTURE



[1]Investigations

- FBC, ESR (If ESR raised, measure serum paraproteins and urine Bence Jones protein)
- Bone and liver function tests (Ca, P, Alk phos, albumin, ALT)
- Renal function
- Serum 25 0H Vit D
  Consider PTH if:
  - Calcium level raised
  - Calcium level in upper quartile of normal range and vitamin D deficient

  Additional tests if indicated:
- Serum TSH
- Coeliac screen (TTG)
- Serum testosterone, LH and SHBG, PSA (men)
- Consider γGT
- Lateral thoracic and lumbar spine X rays
- BMD if monitoring required
- Consider Isotope bone scan

[2]General measures

- Recommend good nutrition esp. with adequate calcium and vitamin D (see link to dietary calcium calculator)[15]
- Recommend regular weight bearing exercise
- Maintain ideal body weight
- Avoid tobacco use and alcohol abuse
- Assess falls risk and give advice if appropriate

Consider any of the following 2nd line treatments if alendronate not suitable because patient

- unable to comply with the special instructions for the administration of alendronate
- has a contraindication to, is intolerant of, or has a lack of clinical response to alendronate

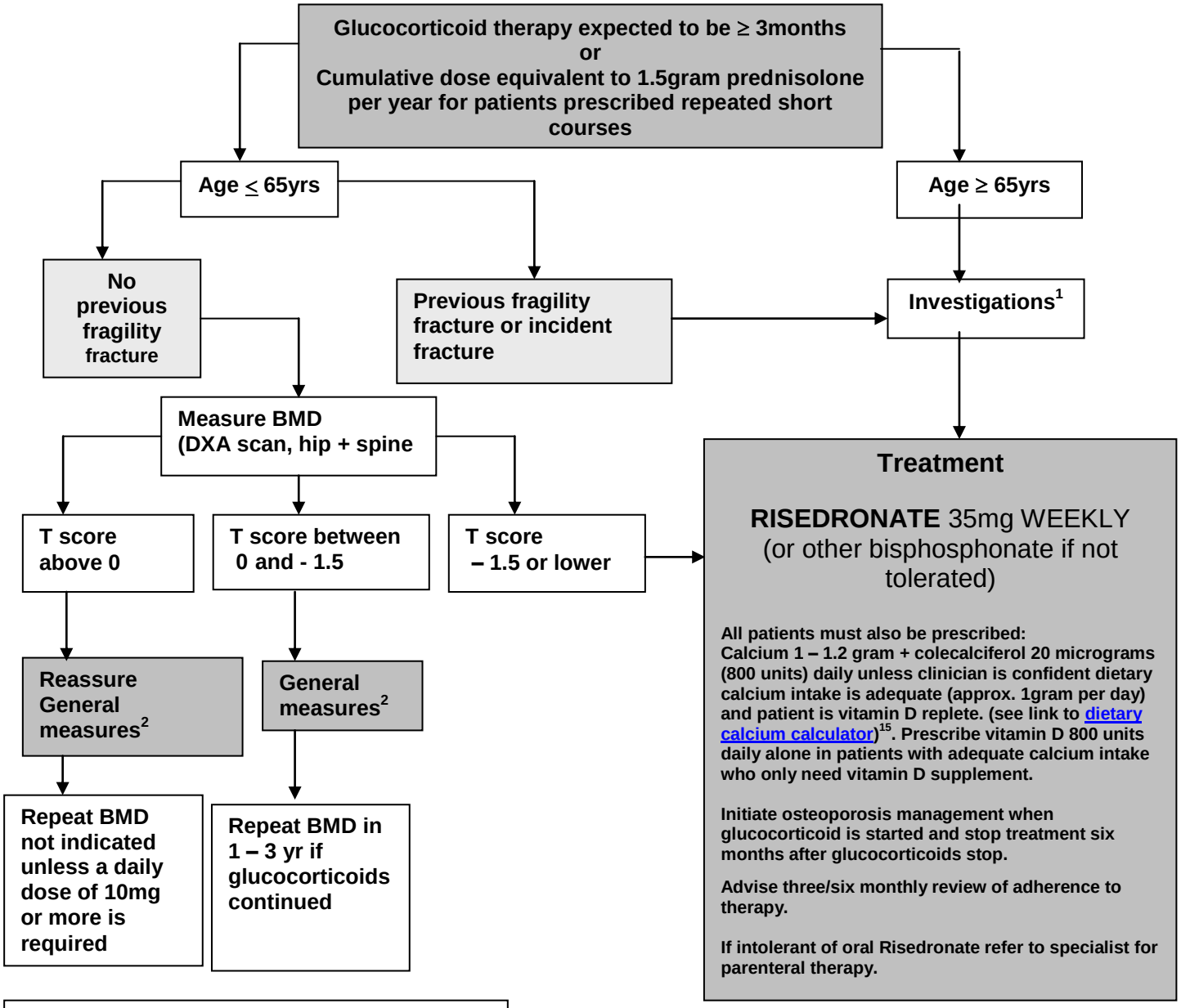
ALTERNATIVE BISPHOSPHONATE	DENOSUMAB	RALOXIFENE	STRONTIUM
(Including intravenous bisphosphonates) Refer to Page 6 and Table A on Page 10 of guidelines	60mg s.c. injection Administered every 6 months Green Drug see GP Information Sheet* Refer to page 7 of guidelines	60mg daily Refer to page 8 of guidelines	2 g at night Restricted indications only Refer to page 8 of guidelines

Specialist Initiated Teriparatide (refer to page 8 of guidelines)

All patients must be prescribed
Calcium 1 – 1.2 gram + colecalciferol 20 micrograms (800 units) daily
unless clinician is confident dietary calcium intake is adequate (approx. 1gram per day) and patient is vitamin D replete. (see link to dietary calcium calculator)[15] Prescribe vitamin D 800 units daily alone in patients with adequate calcium intake who only need vitamin D supplement.

* Please consult the GP Information Sheet [16] at West Hampshire CCG website

ALGORITHM FOR THE MEDICAL MANAGEMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS IN ADULTS



[1]All Patients

- FBC, ESR (If ESR raised, measure serum paraproteins and urine Bence Jones protein)
- Bone and liver function tests (Ca, P, Alk phos, albumin, ALT)
- Renal function
- Serum 25 0H Vit D

Consider PTH if:

- Calcium level raised
- Calcium level in upper quartile of normal range and vitamin D deficient

Additional tests if indicated:

- Serum TSH
- Coeliac screen (TTG)
- Serum testosterone, LH and SHBG, PSA (men)
- Consider γGT
- Lateral thoracic and lumbar spine X rays
- BMD if monitoring required
- Consider Isotope bone scan

[2]General measures

- Reduce dose of glucocorticoid when possible,
- Consider glucocorticoid sparing therapy if appropriate or consider alternative route of administration
- Recommend good nutrition esp. with adequate calcium and vit D (see link to dietary calcium calculator)[15]
- Recommend regular weight bearing exercise
- Maintain ideal body weight
- Avoid tobacco use and alcohol abuse
- Assess falls risk and give advice if appropriate

Clinical Risk Factors For Osteoporosis

- Previous fragility fracture
- Current glucocorticoid use ≥ 3 months and frequer past use
- Parental history of hip fracture
- Radiographic osteopenia
- Height Loss > 3.0 – 5.0 cm
- Female hypogonadism
  - post-menopause
  - untreated premature menopause
  - drug or surgically induced menopause
  - premenopausal amenorrhoea ≥6 months, (ex pregnancy)
- Body Mass Index (<19kg/m^2)
- Caucasian/Asian origin
- Current smoking
- ≥ 3 units alcohol daily
- Male hypogonadism

Predisposing medical conditions

- hyperthyroidism
- rheumatoid arthritis
- type 1 diabetes
- inflammatory bowel disease
- malabsorption/coeliac disease
- prolonged immobility
- organ transplantation
- hyperparathyroidism
- chronic liver disease

Drugs associated with osteoporosis

- anticonvulsants
- antipsychotics
- Depo-Provera, >2yrs treatment
- excessive levothyroxine replacement therapy
- Lithium
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- long-term heparin
- Aromatase inhibitors* (see guidance below)
- GnRH analogues** (see guidance below)
- Proton Pump Inhibitors*** (see guidance below)
- Pioglitazone

*** Aromatase inhibitors (AI)**

(NICE CG80 Early and locally advanced breast cancer: diagnosis and treatment ,and ESMO Clinical Practice Guidelines: Bone Health in cancer patients)[20,2]

1) Patients with early invasive breast cancer should have a baseline DEXA scan to assess bone mineral density if they:

- are starting adjuvant aromatase inhibitor treatment
- have treatment-induced menopause
- are starting ovarian ablation/suppression therapy

2) Offer bisphosphonates to patients identified by Algorithms 1 and 2 (see Appendix 1)[1]

**** Androgen Deprivation Therapy (ADT)**

(NICE CG175 Prostate Cancer Diagnosis and Management, and ESMO Clinical Practice Guidelines: Bone Health in cancer patients)[21,2]

- The use of GnRH analogues in men is associated with bone loss and fractures.
- Assess fracture risk in line with NICE CG146 [4]**.** Offer bisphosphonates to men who are having ADT and have osteoporosis. Consider denosumab if bisphosphonates are contraindicated or not tolerated.
- Monitor BMD at 1 - 2year intervals
- All patients must also be prescribed calcium +colecalciferol daily (see page 6)

*** **Proton Pump Inhibitors[3] –** have been associated with an increased risk of fractures, particularly when used at high doses for over a year in the elderly. Patients at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D (see link to dietary calcium calculator)[15] and if necessary, receive other supplements (see treatment algorithm on page 1 of these guidelines).

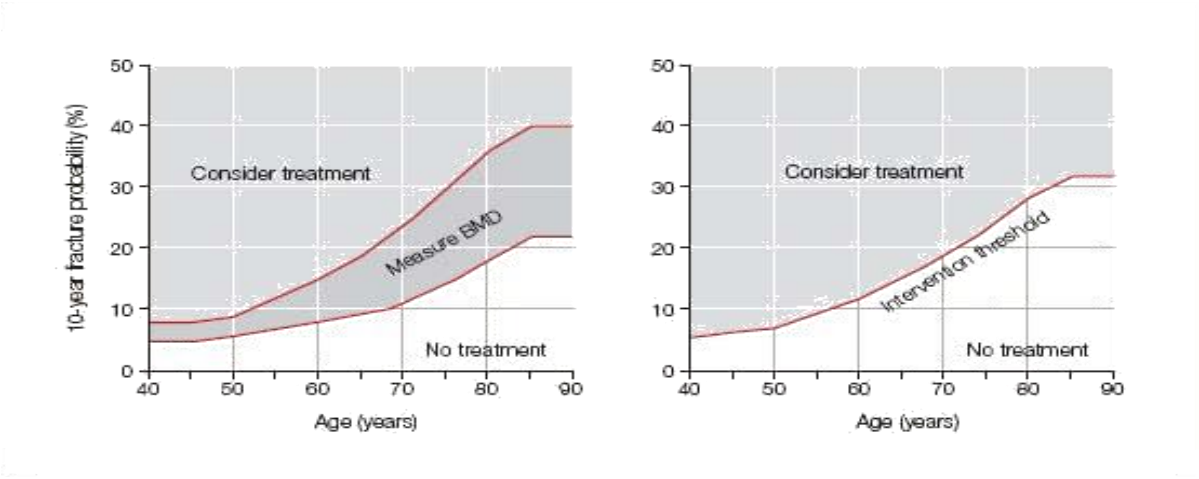
Assessment of Fracture Risk using Frax®

The FRAX® tool is an algorithm which calculates a 10 year fracture risk **for people aged between 40 and 90 years** either with or without BMD values.

10 year probability of major osteoporotic fracture (%)

(Measurement of Bone Mineral Density helps to inform whether treatment is recommended)

Assessment without BMD Assessment with BMD



See

a) www.shef.ac.uk/FRAX and the links to guidance published by the National Osteoporosis Guideline Group (NOGG)[5] for the management of osteoporosis.

b) NICE CG 146 Osteoporosis: assessing the risk of fragility fracture[4]

c) Interpretation and Use of FRAX in Clinical Practice[22]

Anti-fracture efficacy of approved treatments for postmenopausal women with osteoporosis when given with calcium and vitamin D[5]

	Vertebral	Non-vertebral	Hip
Alendronate	**A**	**A**	**A**
Risedronate	**A**	**A**	**A**
Zoledronic Acid	**A**	**A**	**A**
Denosumab	**A**	**A**	**A**
Strontium ranelate	**A**	**A**	**A#**
Teriparatide	**A**	**A**	**nae**
Ibandronate[a]	**A**	**A#**	**nae**
Raloxifene	**A**	**nae**	**nae**
Recombinant human PTH (1-84)	**A**	**nae**	**nae**

in subsets of patients only (post-hoc analysis) nae : not adequately evaluated

[a] Injection only available on Formulary PTH : parathyroid hormone

A evidence levels (Ia meta-analysis of randomised controlled trials (RCTs) and Ib from at least one RCT)

Therapeutic Agents Available For The Management Of Osteoporosis

(See Table on page 5 for anti-fracture efficacy of therapies available)

Refer to the latest data sheet for full prescribing details about use in elderly, renal and hepatic impairment, contraindications, precautions etc.

Refer to the BNF- Guidance on prescribing in renal impairment- for advice on using eGFR / calculated creatinine clearance to adjust doses for patients with renal impairment.

Calcium and Vitamin D_3

Adequate levels of calcium and vitamin D_3 (colecalciferol) are required to ensure optimum effects of all the treatments for osteoporosis (see link to dietary calcium calculator)[15]. Unless the clinician is confident that the patient has adequate calcium intake and is vitamin D replete, calcium and colecalciferol supplementation at a dose of Calcium 1 – 1.2 gram (equivalent to 2.5 – 3.0g Calcium Carbonate) and colecalciferol 20 micrograms (800 units) daily should be prescribed. **Prescribe vitamin D 800 units daily alone in patients with adequate calcium intake (approx. 1gram per day) who only need vitamin D supplementation.** If patient is vitamin D depleted (<25nmol/L) refer to guidelines on supplementation on Map of Medicine. Ensure repletion before starting treatment for osteoporosis.

Avoid colecalciferol in severe renal impairment as it cannot be converted to its active form in the renally impaired.

Bisphosphonates

- Alendronate is the first choice bisphosphonate for the majority of patients
- Risedronate may be prescribed, in patients intolerant of alendronate, in young adults and in patients with glucocorticoid-induced osteoporosis where it may be advantageous due to rapid 'on/off' effect
- Intravenous bisphosphonates may be used under specialist guidance e.g. if oral bisphosphonates are not tolerated or there are compliance issues

Oral bisphosphonates should be swallowed whole with a glass of water 30-60 minutes before the first food or drink (other than water) of the day. Patients should stand or sit upright (not lie down) for at least 30 minutes post dose.

Discontinue treatment if oesophageal ulceration, erosion, stricture, or other severe gastrointestinal symptoms occur.

Bisphosphonates should be avoided in patients with moderate to severe renal impairment.

(eGFR < 35ml/min/1.73m^2 for alendronate, < 30ml/min/1.73m^2 for risedronate and Calculated Creatinine Clearance < 35ml/min for Zoledronate)

Atypical femoral fractures (often bilateral) have been reported rarely with bisphosphonate therapy[7], mainly in patients receiving long-term treatment for osteoporosis. Patients should be advised to report any unexpected thigh, hip or groin pain. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated. (Refer to orthopaedics if necessary). For general advice on duration of therapy see page 9 of these guidelines.

Osteonecrosis of the jaw (ONJ) has been reported rarely with IV bisphosphonate use and very rarely with oral use[6]. Adequate oral hygiene should be maintained during and after bisphosphonate treatment. In patients with concomitant risk factors e.g. cancer, chemotherapy treatment, glucocorticoid treatment, or poor oral hygiene. Remedial dental work should ideally be completed before starting bisphosphonates. Any invasive dental work undertaken whilst taking bisphosphonates will require closer monitoring of the healing process.

Osteonecrosis of the external auditory canal has been very rarely reported[23] with both oral and IV bisphosphonates, mainly in association with therapy of 2 years or longer, with or without additional risk factors e.g. steroid use, chemotherapy, infection, or ear operation. Patients should be advised to report any ear symptoms whilst on bisphosphonate therapy.

Denosumab

(Status Green since December 2015)

Treatment will be initiated for in-patients, or recommended for out-patients in secondary care. GPs may initiate denosumab therapy in line with current DPC approved local guidance.

(Please consult the GP Prescribing Information Sheet [16] at West Hampshire CCG website)

Indicated for:-

1) Treatment of osteoporosis when bisphosphonates inappropriate, or if a fracture sustained whilst on bisphosphonate therapy, in:
   a) postmenopausal women
   b) men at increased risk of fractures
2) Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, when bisphosphonates inappropriate.

- Hypocalcaemia is a **contraindication** to Denosumab therapy. Check serum calcium and correct pre-existing hypocalcaemia before initiating Denosumab and before each dose.
- Ensure adequate intake of calcium and vitamin D (see link to dietary calcium calculator)[15] in all patients receiving denosumab (unless hypercalcaemic) [8].
- Administered as a 60mg subcutaneous injection (at any time of day) at 6 month intervals. Hospital to inform GP of the date of administration of denosumab injection, and GP to set up a recall for future doses at 6 month intervals, to add denosumab to patient's repeat prescription and to remove other osteoporosis treatments (e.g. bisphosphonates, strontium).
  (*Guidance on set up of recall systems available from Medicines Management Team).*
- No dose adjustment required in patients with renal impairment, but check renal function prior to each dose to identify those that may be predisposed to hypocalcaemia. For patients predisposed to hypocalcaemia [e.g. severe renal impairment (creatinine clearance < 30ml/min; eGFR 15 – 29ml/min/1.73m^2) or on dialysis] recheck serum calcium within two weeks and 3 months after each dose or more frequently if clinically indicated[18].

Osteonecrosis of the jaw (ONJ)[18] has been reported (rarely) in patients receiving denosumab for osteoporosis (most cases occur in cancer patients prescribed the 120mg dose). Give patient the **Denosumab Patient Reminder Card[19] which contains advice about ONJ.** Patients should avoid invasive dental procedures during treatment if possible. Regular dental check-ups are recommended in patients on denosumab. If invasive dental work is undertaken whilst the patient is on denosumab therapy, closer monitoring of the healing process will be necessary.

Atypical femoral fractures have been reported rarely during long-term (≥2.5 years) treatment[9]. Any patient presenting with unexpected thigh, hip or groin pain should be evaluated for an incomplete femoral fracture. Discontinuation of denosumab therapy should be considered if an atypical femur fracture is suspected, while the patient is evaluated. (Refer to orthopaedics if necessary).

Be aware that bone loss is rapid on discontinuation of denosumab therapy, therefore a 'drug holiday' is not appropriate.

Strontium Ranelate[17]

For the treatment of severe osteoporosis (T-score at least -2.5, plus fragility fracture)

- In men and postmenopausal women at high risk of fracture

  for whom treatment with other osteoporosis medication is not possible due to contra-indications, intolerance, or inability to adhere to strict regimen.

Contra-indicated if medical history of

- Current or past history of ischaemic heart disease
- Peripheral arterial disease
- Cerebrovascular disease
- **Uncontrolled** hypertension
- Current or previous venous thromboembolism (VTE), temporary or permanent immobilisation

- Re-assess individual patient's cardiovascular and VTE risks every 6 to 12 months and stop if the risks significantly increase.

Avoid in severe renal impairment (eGFR $<$ 30ml/min/1.73m^2).

Strontium should be taken at bedtime at least 2 hours after food and/or milk.

Severe allergic reactions including DRESS (drug rash with eosinophilia systemic symptoms) have been reported in patients taking strontium. If a rash develops, treatment must be stopped permanently, and the DRESS symptoms treated appropriately.

Raloxifene

Selective oestrogen receptor modulator (SERM)

For postmenopausal women with vertebral osteoporosis, with an unsatisfactory response to or an intolerance of bisphosphonates. **Avoid in severe renal impairment.**

Teriparatide (Specialist Use only)

Indications restricted to patients with an unsatisfactory response/intolerance to the above therapies **and**

- aged $\geq$ 65 yrs old who have a T score of –4 SD or below **or**
- aged $\geq$ 65 yrs old who have a T score of -3.5 SD or below **plus** at least 2 fractures **or**
- aged 55 – 64 yrs old who have a T score of -4 SD or below **plus** at least 2 fractures

Use with caution in moderate renal impairment. Contraindicated in severe renal impairment.

Hormone Replacement Therapy

recommended as treatment for the prevention of osteoporosis in women with a premature menopause (up to 50 years of age).

Combination Therapy

(not including combinations with Calcium and colecalciferol)

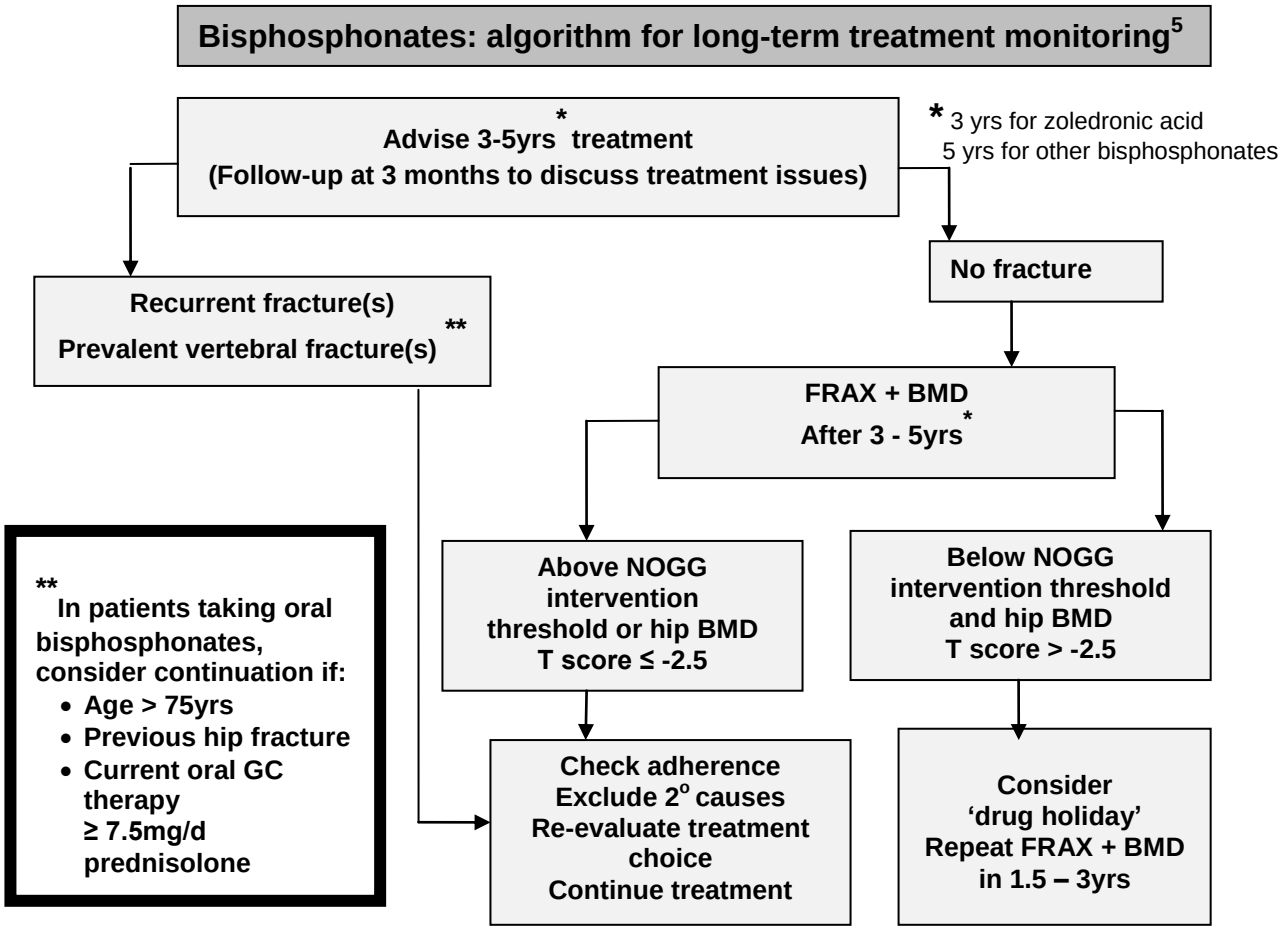
- is not routinely prescribed but may be rarely used under specialist recommendation

Duration Of Treatment

Review and reassess all patient's fracture risk at intervals during treatment (use FRAX® +/- DXA). Ensure patient is calcium and vitamin D replete (see link to dietary calcium calculator)[15], or continue adequate supplementation).

Oral bisphosphonates – review after 5 years and follow the algorithm below:

(additional information available for oral bisphosphonates on pages 9-10 in the NOGG guideline NOGG Clinical Guideline for prevention and treatment of Osteoporosis)[5]



Denosumab – review after 5 years, and continue therapy if indicated. Be aware that bone loss is rapid on discontinuation of denosumab therapy, therefore a 'drug holiday' is not appropriate.

Raloxifene and Strontium ranelate– review and reassess after up to five years of treatment and continue if indicated. (In addition, patients prescribed strontium ranelate also require a review of CVD and VTE risk profile every 6 to 12 months).

Teriparatide should be used for a maximum of 24 months.

Zoledronic acid – review after 3 years and follow the algorithm above: (additional information for zoledronic acid available on pages 9-10 in the NOGG guideline NOGG Clinical Guideline for prevention and treatment of Osteoporosis)[5].

For patients identified at high risk of fracture following an individual risk assessment, it appears safe to continue for a further five years (three years for zoledronic acid) of treatment then reassess. At present there is good data to support continued use for 10years.

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2. R Coleman et al. Bone Health in cancer patients: ESMO Clinical Practice Guidelines. Annals of Oncology Vol. 25(Supplement3) iii124-iii137 September 2014
3. MHRA Drug Safety Update April 2012, vol 5 issue 9: A2 Proton pump inhibitors in long term use: increased risk of fracture.
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16. Basingstoke, Winchester & Southampton District Prescribing Committee Denosumab Prescribing Information Sheet for GPs. February 2016 at West Hampshire CCG website
17. HRA Drug Safety Update Volume 7, Issue 8 March 2014 Strontium ranelate: cardiovascular risk—restricted indication and new monitoring requirements.
18. MHRA Drug Safety Update Volume 8, Issue 2 September 2014 A2 Denosumab: updated recommendations. Minimising the risk of osteonecrosis of the jaw; monitoring for hypocalcaemia.
19. MHRA Drug Safety Update Volume 8, Issue 12 July 2015 Denosumab (Xygeva▼,Prolia) ; intravenous bisphosphonates: osteonecrosis of the jaw - further measures to minimise risk.
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21. NICE Clinical Guideline CG175 Prostate Cancer Diagnosis and Management (Jan 2014)
22. Kanus J.A et al. Interpretation and use of FRAX in clinical Practice. Osteoporosis International (2011) 22:2395-2411.
23. MHRA Drug Safety Update Volume 9, Issue 5 December 2015. Bisphosphonates: very rare reports of osteonecrosis of the external auditory canal.

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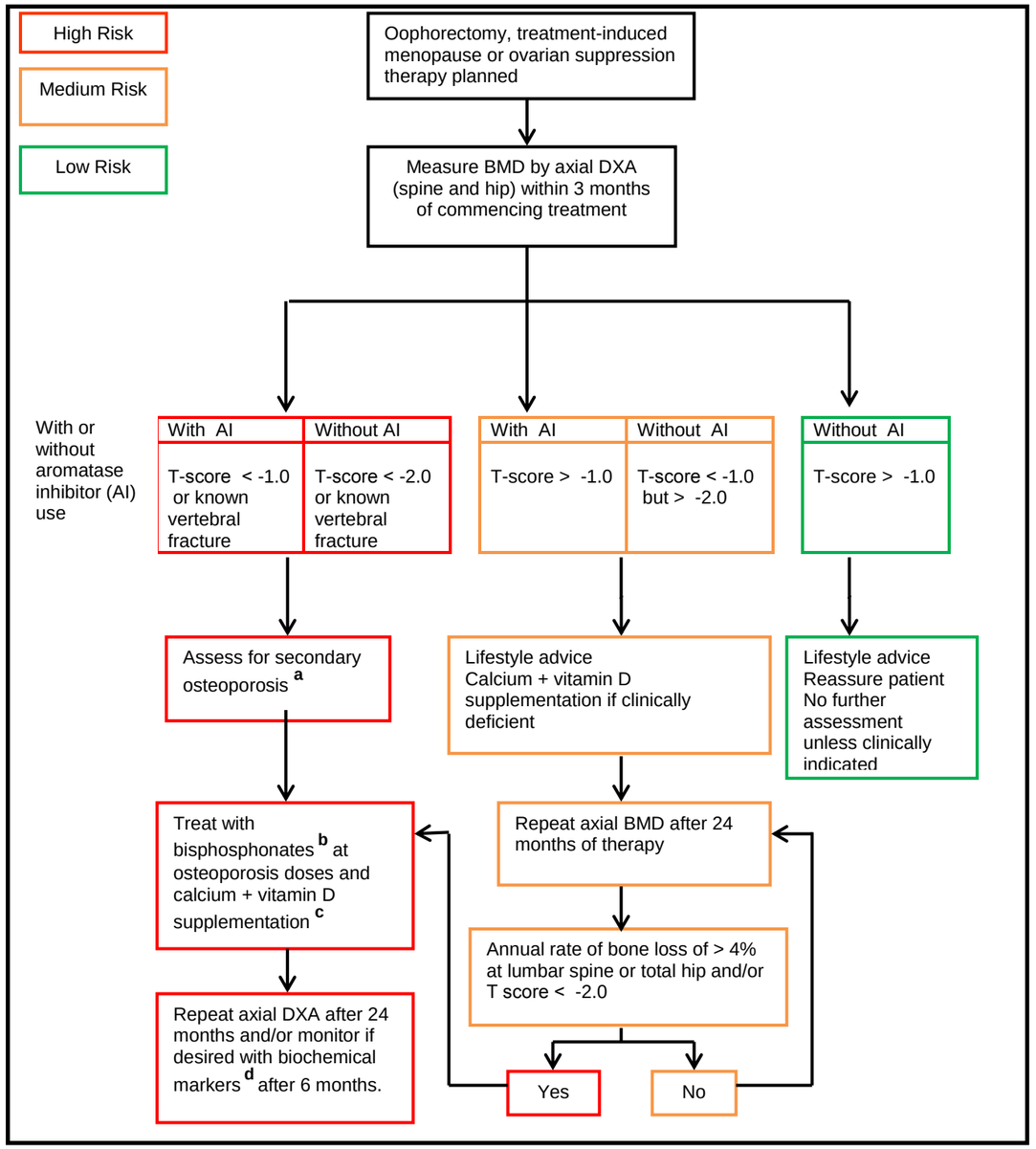
Approved by:	**Basingstoke Southampton and Winchester District Prescribing Committee** **Date : February 2016 (Amended Feb 2017) Review Date February 2018**

Appendix 1 Management of bone loss in early breast cancer

Algorithm 1: Adjuvant treatment associated with ovarian suppression/failure with or without concomitant aromatase inhibitor use in women who experience premature menopause.



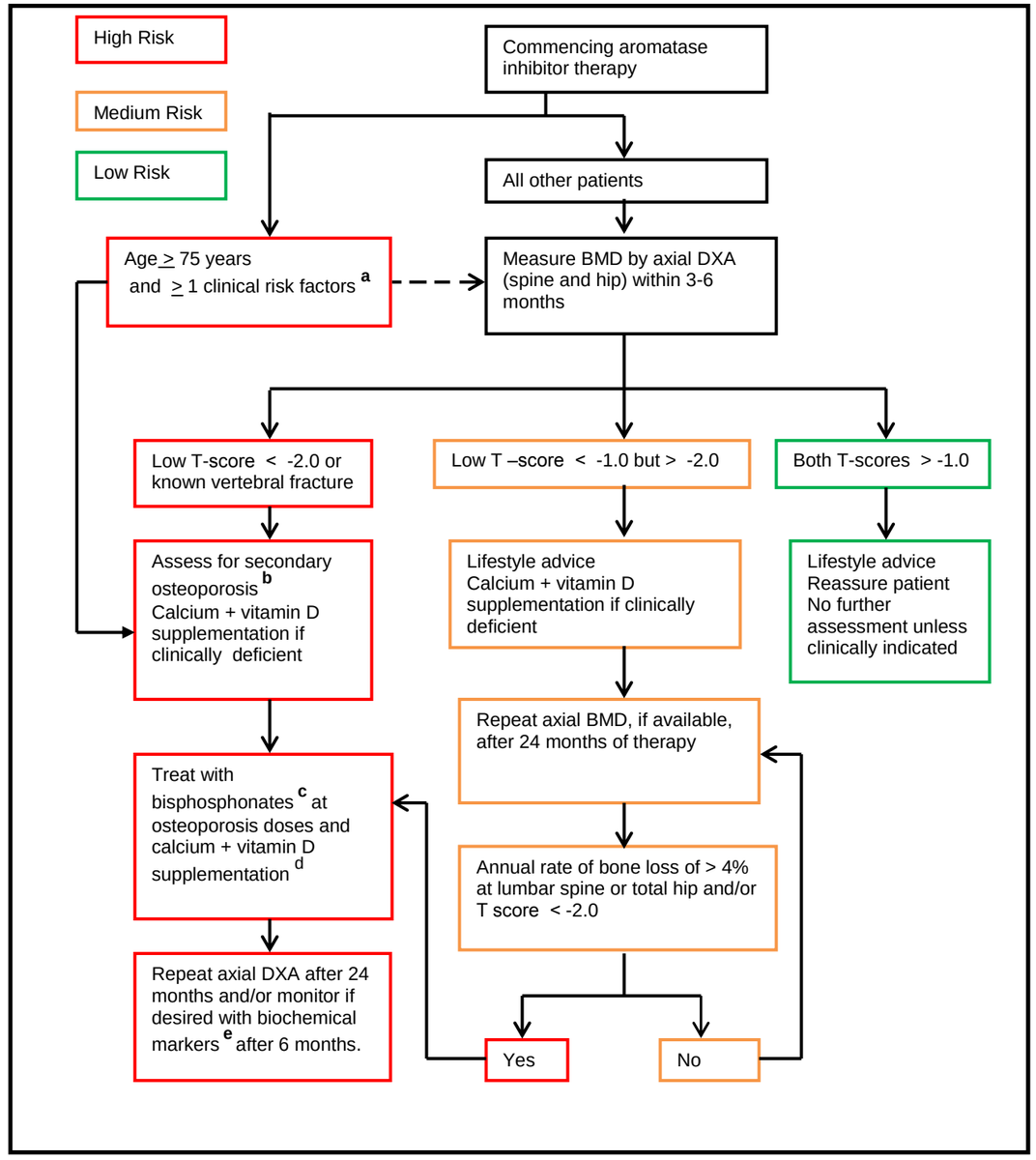
a ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST / ɣGT), serum creatinine, endomysial antibodies, serum thyroid stimulating hormone.
b Alendronate 70mg per week, risedronate 35mg per week, ibandronate (150mg po monthly or 3mg iv 3-monthly), zoledronic acid 4mg iv 6-monthly.
c To be given as ≥ 1 g of calcium + ≥ 800 IU of vitamin D.
d Biochemical markers such as serum C-terminal telopeptide of type 1 collagen or urinary N-telopeptide of type 1 collagen

Reference

Reid DM, Doughty J, Eastell R, Heys SD, Howell A, McCloskey EV, Powles T, Selby P, Coleman RE. Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. 2008. Cancer Treat Rev 2008;34:S1–S18.

See also R Coleman et al. Bone Health in cancer patients: ESMO Clinical Practice Guidelines. Annals of Oncology Vol. 25 (Supplement3) iii124-iii137 September 2014

Algorithm 2: Postmenopausal adjuvant treatment with aromatase inhibitors.



a Previous low trauma fracture after age 50, parental history of hip fracture, alcohol intake of ≥ 4 units / day, diseases associated with secondary osteoporosis, prior corticosteroids for > 6 months, low BMI (<22).
b ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST / ɣGT), serum creatinine, endomysial antibodies,serum thyroid stimulating hormone.
c Alendronate 70mg per week, risedronate 35mg per week, ibandronate (150mg po monthly or 3mg iv 3-monthly), zoledronic acid 4mg iv 6-monthly.
d To be given as ≥ 1 g of calcium + ≥ 800 IU of vitamin D.
e Biochemical markers such as serum C-terminal telopeptide of type 1 collagen or urinary N-telopeptide of type 1 collagen