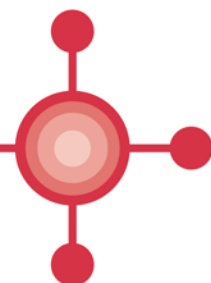


All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan



# **Guidance to Support the Safe Use of Long-term Oral Bisphosphonate Therapy**

September 2015

This report has been prepared by a multiprofessional collaborative group, with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC), and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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## 1.0 INTRODUCTION

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Recent data have suggested that the longer-term use of oral bisphosphonate treatment (particularly > five years) may be associated with increased risk of drug-related side effects, particularly atypical femur fracture<sup>1</sup>. This was the subject of Medicines and Healthcare Products Regulatory Agency (MHRA) guidance issued in 2011 (Appendix 1)<sup>1</sup>. These fractures are significant events and have been predominantly reported in patients receiving long-term bisphosphonate treatment for osteoporosis (see [Glossary](#)). Discontinuation of bisphosphonate therapy in patients suspected as having an atypical femur fracture should be considered and further future treatment for osteoporosis should proceed only after a careful assessment of the benefits and risks of continuing treatment<sup>1</sup>, ideally by a specialist.

The MHRA advised that: “The need for continued [bisphosphonate] treatment [for osteoporosis] should be re-evaluated periodically based on the benefits and potential risks of bisphosphonate therapy for individual patients, particularly after five or more years of use”<sup>1</sup>. However, this has not generally led to active review of patients in primary care. The scale of this issue in Wales is supported by Welsh pilot audit data, which suggest that 1.7% of a practice population may be prescribed bisphosphonate therapy with a significant minority (44%) continuing on treatment for more than 5 years (Appendix 2).

Work undertaken by the Bone Research Unit in Cardiff and Vale University Health Board has to date reviewed 950 patients, from 41 GP practices, who are over the age of 50 and have been taking an oral bisphosphonate for at least four years. Over 60% have stopped their bisphosphonate treatment on the basis of long-term use. Fifty percent require a bone density scan to determine future management.

National Osteoporosis Guideline Group (NOGG) guidance was issued in 2013 and includes a suggested algorithm for long-term treatment monitoring and review of patients on bisphosphonate therapy<sup>2</sup>. Whilst it is recognised that NOGG is an expert body, comprising a number of UK opinion leaders in osteoporosis, its guidance would not carry the same weight as that from a national regulatory body and is not yet supported by a solid evidence base at every step.

## 2.0 ASSESSMENT OF FRAGILITY FRACTURE RISK

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Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture<sup>3</sup>. NICE recommend a targeted approach to assess fracture risk<sup>3</sup>.

Consider assessment of fracture risk:

- In all women aged 65 years and over and all men aged 75 years and over
- In women aged under 65 years and men aged under 75 years in the presence of risk factors, for example:
  - previous fragility fracture (see [Glossary](#))
  - 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 18.5 kg/m<sup>2</sup>)
  - smoking
  - alcohol intake of more than 14 units per week for women and more than 21 units per week for men<sup>3</sup>.

People under 50 years should not routinely be assessed for fracture risk, unless they have major risk factors (for example, current or frequent recent use of oral or systemic glucocorticoids, untreated premature menopause or previous fragility fracture), as they are unlikely to be at high risk<sup>3</sup>.

Osteoporotic fracture risk is calculated using an assessment tool that calculates risk based on a person's risk factors (the predicted risk of major osteoporotic or hip fracture over 10 years, expressed as a percentage). Recommended tools include the WHO Fracture Risk Assessment Tool (FRAX<sup>®</sup>, see [Glossary](#)) and QFracture<sup>®</sup> (see [Glossary](#)). Both tools can be used to calculate risk without a bone mineral density (BMD) measurement. (BMD values cannot be incorporated into QFracture<sup>®</sup>.) The predicted 10-year fracture risk calculated using FRAX<sup>®</sup> (without a BMD value) or QFracture<sup>®</sup> can be used to determine whether treatment or further assessment, by measuring BMD with (DXA) (see [Glossary](#)), is appropriate<sup>3</sup>.

- People at high risk may be offered treatment without further assessment (for example, those > 75 years of age with a classical fragility fracture).
- People at intermediate risk are offered a DXA scan and their fracture risk recalculated incorporating their BMD to more accurately determine their fracture risk using FRAX<sup>®</sup>. People found to be above the treatment threshold are offered treatment.
- People at low risk are not offered treatment or a DXA scan.

### 3.0 LIFESTYLE ADVICE

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All people at risk of, or with, osteoporosis should be provided with lifestyle advice to help maintain bone strength.

- Exercise regularly (within limits imposed by underlying disease) – Weight-bearing exercises (activities where the feet and legs support the body's weight) e.g. walking, running and keep-fit classes are essential to maintaining bone health.
- Eat a balanced, healthy diet – Ensure enough calcium and vitamin D. Certain foods provide excellent sources of calcium, while diets high in protein and/or sodium increase calcium loss.
- Ensure adequate calcium intake – Calcium plays a key role in keeping bones strong. Calcium-rich foods include leafy green vegetables, dried fruit, tofu and dairy products.
- Vitamin D is also essential, as it helps ensure absorption and retention of calcium in bones. Vitamin D can be found in eggs, milk and oily fish; however, most vitamin D is made in the skin in response to sunlight. Short exposure to sunlight without wearing sunscreen (10 minutes twice a day) throughout the summer should provide you with enough vitamin D for the whole year.
- Give up smoking – Smoking has a detrimental effect on bone density, leading to greater risk of injury and longer recovery times.
- Limit alcohol consumption – The exact way alcohol affects bone isn't entirely understood; however, excessive alcohol use has been shown to accelerate bone loss. The recommended daily limit is 3–4 units of alcohol for men and 2–3 units for women.

People aged 65 and older have the highest risk of falling, with 30% of people older than 65 falling at least once a year<sup>4</sup>. People with osteoporosis are more likely to have a fracture if they fall, therefore advice should be given on falls prevention, such as making a safe home environment without trip hazards and wearing well fitting footwear. NICE CG146 recommends considering assessment of fracture risk in all women over the age of 65 and men over 75, and younger people in the presence of risk factors<sup>3</sup>.

Adequate calcium and vitamin D intake is essential in people prescribed bisphosphonates, as bisphosphonates require calcium and vitamin D in the body to achieve maximum effect.

#### 4.0 TREATMENT FOR PEOPLE AT HIGH RISK OF AN OSTEOPOROTIC FRACTURE

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- Women who have experienced a premature menopause (menopause before 45 years of age) should be offered treatment with hormone replacement therapy (HRT) to reduce their risk of osteoporotic fracture, and for the relief of menopausal symptoms<sup>5</sup>. HRT should be continued up until 50 years of age and then stopped, and the need for continuing treatment with an alternative drug considered<sup>5</sup>.
- For premenopausal women and men less than 50 years who have had an osteoporotic fracture, refer for specialist management<sup>5</sup>.
- Postmenopausal women and men over 50 years of age who are at high risk of an osteoporotic fracture should be offered treatment with a bisphosphonate<sup>5</sup>. This treatment is usually given for 3 years (zoledronic acid) to 5 years (alendronate, risedronate); it reduces, but does not eliminate, the risk of osteoporotic fracture. Choice should take into account cost-effectiveness.
  - Prescribe alendronate first-line for most people<sup>\*</sup>.
  - Consider risedronate second-line for people who cannot tolerate alendronate.
  - Consider specialist referral for people who cannot take or tolerate alendronate or risedronate<sup>5</sup>.
- Specialist treatment options include strontium ranelate, raloxifene<sup>6</sup>, denosumab<sup>7</sup>, or teriparatide<sup>6,8</sup>. Choice of treatment should take into consideration their costs and adverse effect profile<sup>5</sup>. Alternative treatment options also include a third oral bisphosphonate, ibandronic acid and an injectable bisphosphonate, zoledronic acid, although neither medicine has undergone appraisal by NICE or AWMSG.
- HRT is recommended by the National Osteoporosis Society for women under the age of 60 years when the benefits of treatment outweigh the risks<sup>2</sup>. A NICE Clinical Knowledge Summary considers this to be the case when non-oestrogen treatments are unsuitable and there is a significant risk of a fragility fracture<sup>5</sup>.

An analysis of randomised controlled trial data identified an increased risk of serious cardiac disorders, including myocardial infarction (although no increased risk in mortality was observed) in patients taking strontium ranelate (Protelos<sup>®</sup>)<sup>9</sup>. As a consequence the European Medicines Agency (EMA) has restricted the use of strontium ranelate to patients who cannot take other medicines approved for the treatment of osteoporosis, and have no history of heart and circulatory problems<sup>10</sup>. The MHRA have updated their advice, also recommending that the risk of cardiovascular disease should be assessed before starting treatment and that people with ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and uncontrolled hypertension should not be initiated on strontium ranelate. Treatment with strontium ranelate should be reviewed and discontinued in an individual who develops any of these conditions<sup>11</sup>.

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<sup>\*</sup>See Appendix 3 for a plain language patient summary of a Cochrane review on the effect of alendronate for preventing fractures caused by osteoporosis.

## 5.0 THE BENEFITS OF ORAL BISPHOSPHONATE THERAPY

Evidence shows that the patients most likely to benefit from treatment with bisphosphonates are women who have already been diagnosed with low BMD or have already had a vertebral fracture. The number of patients that are needed to treat (NNT) using alendronate plus calcium/vitamin D for secondary prevention of a vertebral or hip fracture is given in Table 1.

**Table 1. NNTs for secondary prevention of vertebral and hip fractures using alendronate + calcium/vitamin D (taken from NHS Highland Guidance for prescribing in frail adults<sup>12</sup>)**

Age	Secondary prevention of vertebral fracture (NNT) <sup>§</sup>	Secondary prevention of hip fracture (NNT) <sup>§</sup>
70–74 years	65	430
75–79 years	45	180
80–84 years	60	105
85–89 years	55	45
≥ 90 years	40	40

<sup>§</sup> Number of patients needed to be treated for one year to prevent a fracture

## 6.0 THE RISKS OF ORAL BISPHOSPHONATE THERAPY

Oral bisphosphonates can cause undesirable effects; for example, the SPC for alendronic acid lists the following, many of which are class effects:

- Very common (occurring for  $\geq 1/10$  patients): musculoskeletal (bone, muscle or joint) pain which is sometimes severe.
- Common (occurring for between  $\geq 1/100$  and  $< 1/10$  patients): headache, abdominal pain, dyspepsia, constipation, diarrhoea, flatulence, oesophageal ulcer, dysphagia, abdominal distension, acid regurgitation.
- Uncommon (occurring for between  $\geq 1/1,000$  and  $< 1/100$  patients): nausea, vomiting, gastritis, oesophagitis, oesophageal erosions, melena, eye inflammation (uveitis, scleritis, episcleritis), rash, erythema.
- Rare (occurring for between  $\geq 1/10,000$  and  $< 1/1,000$  patients): hypersensitivity reactions including urticaria and angioedema, oesophageal stricture, oropharyngeal ulceration, upper gastrointestinal perforation, ulcers and bleeding, rash with photosensitivity, severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, hypocalcaemia, osteonecrosis of the jaw, atypical subtrochanteric and diaphyseal femoral fractures<sup>13</sup>.

### 6.1 Osteonecrosis of the jaw

Osteonecrosis of the jaw is a very rare event that occurs predominantly in cancer populations with use of intravenous bisphosphonates. However, it has been reported in the osteoporosis population with oral bisphosphonate use<sup>14</sup>.

### 6.2 Atypical femur fractures

Atypical subtrochanteric and diaphyseal femoral fractures are rare events, the absolute number reported being far lower than the number of osteoporotic fractures prevented<sup>14</sup>. The data suggest a strong association with bisphosphonate use, although causality has not been determined. The overall balance of risks and benefits of individual bisphosphonates in their authorised indications remains favourable<sup>14</sup>.

Complete fractures are clinically obvious, with immediate hospital admission required. However, 'incomplete' fractures can occur, with some people experiencing pain weeks to months before presenting with a completed fracture. People taking bisphosphonates are advised to report any pain in the thigh, hip, or groin. If following medical assessment an incomplete atypical fracture is suspected, radiography of the femur should be arranged<sup>15</sup>.

Because of concerns about rare but serious side effects of long-term antiresorptive therapy, many physicians prescribe these drugs for a finite period of time, usually three years (zoledronic acid) to five years (alendronate, risedronate). Reassessment of fracture risk at the end of this treatment period is important, since some people remain at high risk of fracture and require continued treatment, whereas others may benefit from a 'drug holiday' for one or more years<sup>3</sup>.

## 7.0 ADVICE FOR PEOPLE TAKING ORAL BISPHOSPHONATES

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- Patients should be encouraged to keep taking the bisphosphonate. Adherence declines significantly after the first year of treatment.
- If their dietary calcium intake and vitamin D status are inadequate, patients should be advised that they will also be prescribed calcium and vitamin D supplementation.
- Bisphosphonates should be taken at least 30 minutes before the first food, other medicinal product, or drink (other than water) of the day.
- Patients should be advised to:
  - stop taking the bisphosphonate and seek medical advice if they experience any signs or symptoms of possible oesophageal reaction, for example dysphagia, pain on swallowing, retrosternal pain, or new/worsened heartburn;
  - have a regular dental check up and to tell their dentist that they are taking a bisphosphonate, particularly if they are going to undertake invasive dental procedures;
  - report any pain in the thigh, hip, or groin, as 'incomplete' atypical femur fractures can occur, with some people experiencing pain weeks to months before presenting with a completed fracture<sup>5</sup>.

## 8.0 BISPHOSPHONATE 'DRUG HOLIDAYS'

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The risks identified with longer-term bisphosphonate use have led to the concept of a 'drug holiday' (see [Glossary](#)) in treatment.

FRAX<sup>®</sup> has been validated as an effective means of reassessment of fracture risk in treated individuals with osteoporosis. FRAX<sup>®</sup> (+/- BMD) can be used to calculate an individual's risk and used alongside NOGG intervention thresholds to guide the decision as to whether treatment can be stopped for a period of time<sup>2</sup>.

QFracture<sup>®</sup> has not been examined in treated patients. It is not known whether the ability of clinical risk factors with or without measurement of BMD to predict fracture risk is similar in untreated and treated patients<sup>3</sup>.

Based on the results of individual patient review at 5 years of treatment, some individuals may be identified with clinical or radiological risk factors that support continuing treatment. These decisions can be informed by the use of DXA scanning, but the NOGG guidance allows for an alternative algorithmic approach, particularly where there is limited DXA availability or it is considered inappropriate.

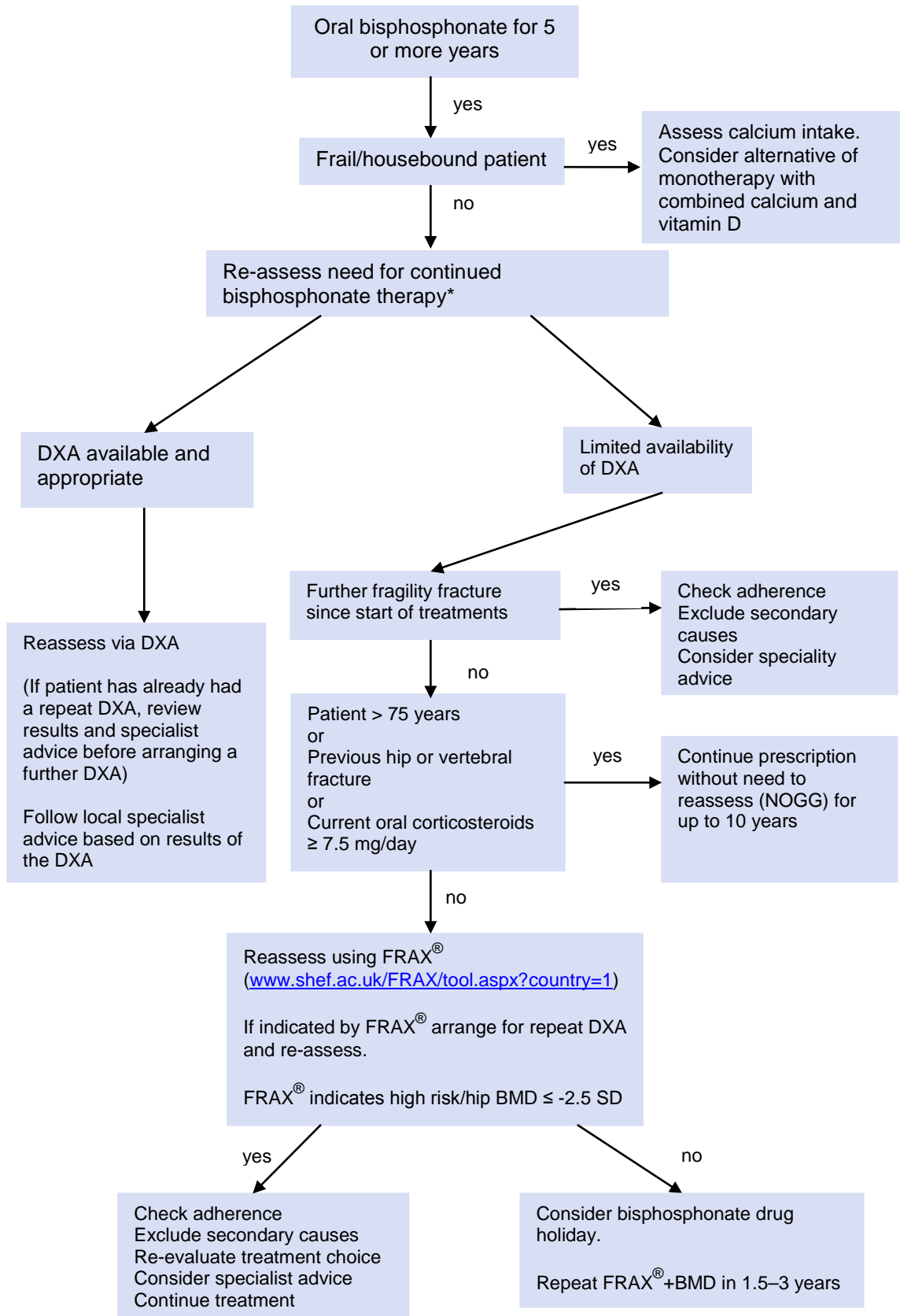
Withdrawal of treatment is associated with decreases in BMD and increased bone turnover after two to three years for alendronate and one to two years for ibandronate and risedronate<sup>2</sup>. Re-assessment of fracture risk should be undertaken at a future, suitable time point. Local expert opinion suggests re-assessment at eighteen months to two years for risedronate and ibandronate, and two to three years for alendronate, unless clinical circumstances suggest an earlier review.

See Appendix 4 for a sample patient information leaflet on drug holidays.



9.0 REVIEW OF LONG-TERM BIPHOSPHONATE THERAPY

Figure 1. Review of oral bisphosphonates for osteoporosis treatment algorithm.



\*see local guidance/resources to determine whether to use FRAX or review using DXA

Following the assessment of fracture risk using FRAX<sup>®</sup> in the absence of BMD measurement, the patient may be classified as being at low, intermediate or high risk. The NOGG intervention thresholds can then be used to guide the decision as to whether treatment can be stopped for a period of time<sup>2</sup>.

- Low risk – Reassure, give lifestyle advice, consider a bisphosphonate ‘drug holiday’
- Intermediate risk – Measure BMD (if not undertaken in previous 12 months).
  - If BMD > -2.5 SD consider bisphosphonate ‘drug holiday’
  - Use FRAX<sup>®</sup> and BMD measurement to recalculate fracture risk. If below the intervention threshold consider bisphosphonate ‘drug holiday’.
- High risk – Continue treatment without the need for BMD assessment, although it may be appropriate to measure BMD in certain clinical situations

Local expert opinion suggests re-assessment at eighteen months to two years for risedronate and ibandronate, and two to three for alendronate, unless clinical circumstances suggest an earlier review.

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## GLOSSARY

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### **FRAX<sup>®</sup> fracture risk assessment tool**

A diagnostic tool, which uses clinical risk factors and BMD at the femoral neck to calculate the ten year probability of hip fracture and ten year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture)<sup>16</sup>.

### **QFracture<sup>®</sup> risk calculator**

A web calculator which uses a patient's answers to simple questions concerning their health status to work out the risk of developing any osteoporotic or hip fracture<sup>17</sup>.

### **Dual-energy X-ray Absorptiometry (DXA) scan**

A DXA scan uses X-rays to measure BMD and diagnose osteoporosis<sup>18</sup>.

### **Osteoporosis**

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture<sup>3</sup>. Osteoporosis is defined as

- A BMD T score of  $\leq -2.5$  SD below the mean peak mass (average of healthy young adults) confirmed by DXA scan<sup>19</sup>;
- In patients > 75 years:
  - For secondary prevention purposes: If a woman aged 75 years or older who has one or more independent clinical risk factors\* for fracture or indicators of low BMD has not previously had her BMD measured, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.
  - For primary prevention purposes: If a woman aged 75 years or older who has two or more independent clinical risk factors for fracture or indicators of low BMD<sup>†</sup> has not previously had her BMD measured, a DXA scan may not be required if the responsible clinician considers it to be clinically inappropriate or unfeasible.

### **Fragility fractures**

Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level (or 'low energy') trauma<sup>3</sup>. The World Health Organization (WHO) has quantified this as forces equivalent to a fall from a standing height or less. Fractures of the small bones of hands and feet, scaphoid fractures and avulsion fractures would not commonly be classified as fragility fractures.

### **Drug holiday**

A drug holiday is when a patient stops taking a medication(s) for a period of time, ranging from a few days to many months or years.

\*Independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of four or more units per day, and rheumatoid arthritis.

<sup>†</sup>Indicators of low BMD are low body mass index (defined as less than 22 kg/m<sup>2</sup>), medical conditions such as ankylosing spondylitis, Crohn's disease, conditions that result in prolonged immobility, and untreated premature menopause.

## APPENDIX 1. DRUG SAFETY ADVICE (FROM MHRA DRUG SAFETY UPDATE<sup>1</sup>)

### Drug safety advice

#### Bisphosphonates: atypical femoral fractures

##### Summary

Atypical femoral fractures have been reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated, and should be based on an assessment of the benefits and risks of treatment. The need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on the benefits and potential risks of bisphosphonate therapy for individual patients, particularly after 5 or more years of use.

Individual bisphosphonates have different indications, and are used for: prophylaxis and treatment of osteoporosis; treatment of Paget's disease; and as part of some cancer regimens, particularly for bone metastases and multiple myeloma.

In 2008, a Europe-wide review of bisphosphonates and atypical stress fractures concluded that alendronic acid use was associated with an increased risk of atypical stress fractures of the proximal femoral shaft and a warning was subsequently added to alendronic acid product information. At that time, the available data neither supported nor refuted a possible class effect, and the issue was kept under close review and any emerging data evaluated.

A further Europe-wide review has now been completed, which included data from the published literature and that provided by the marketing authorisation (licence) holders (including preclinical studies, clinical trials, and case reports) as well as reports produced by professional organisations.<sup>i,ii</sup> The key findings and advice for healthcare professionals from this review are given below.

##### Key findings:

- 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.
- They can occur after minimal or no trauma – some patients experience thigh or groin pain, often associated with features of stress fractures on radiograph, weeks to months before presenting with a completed femoral fracture; poor healing of these fractures has been reported.
- The overall balance of risks and benefits of individual bisphosphonates in their authorised indications remains favourable – the absolute number of atypical fractures reported is far lower than the number of osteoporotic fractures prevented<sup>iii</sup>

##### Advice for healthcare professionals:

- Atypical femoral fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture.
- Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated, and should be based on an assessment of the benefits and risks of treatment for the individual.
- 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.
- The optimum duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of bisphosphonate therapy for individual patients, particularly after 5 or more years of use.

The risk of atypical femoral fractures with bisphosphonates will be kept under close review in Europe.

To facilitate future case reporting and research, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has adopted a definition of atypical femoral fracture based on the American Society for Bone and Mineral Research (ASBMR) provisional case definition of atypical femoral fracture<sup>i</sup> – major and minor features:<sup>a</sup>

Major features<sup>b</sup>

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with no trauma or minimal trauma, as in a fall from a standing height or less
- Transverse or short oblique configuration
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex

Minor features

- Noncomminuted
- Localised periosteal reaction of the lateral cortex<sup>c</sup>
- Generalised increase in cortical thickness of the diaphysis
- Prodromal symptoms such as dull or aching pain in the groin or thigh
- Bilateral fractures and symptoms
- Delayed healing
- Comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia)
- Use of pharmaceutical agents (e.g., bisphosphonates, glucocorticoids, proton pump inhibitors)

(a) Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumours, and periprosthetic fractures.

(b) All major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required, but sometimes have been associated with these fractures.

(c) Often referred to in the literature as 'beaking' or 'flaring'.

**References**

i Shane E, et al. J Bone Miner Res 2010; 25: 2267–94.

ii Rizzoli R, et al. Osteoporos Int 2011; 22: 373–90.

iii Schilcher J and Aspenberg P. N Engl J Med 2011; 364 : 1728–37.

## APPENDIX 2. PILOT PROJECT TO EXPLORE THE VOLUME OF LONG-TERM BISPHOSPHONATE AND THE OUTCOMES OF REVIEW IN PRIMARY CARE

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Long-term antiresorptive therapy (usually a bisphosphonate) is recognised as an effective anti-fracture therapy in patients with osteoporosis, particularly in patients at high risk of fracture. It has become increasingly apparent however that the longer-term use of such therapies can result in unusual but significant drug-related side effects such as osteonecrosis of the jaw and atypical femur fracture. In light of this, recent expert opinion has suggested the need to reassess the continuing need for bisphosphonate therapy on a patient-by-patient basis beyond five years of use.

Aneurin Bevan University Health Board osteoporosis service offers open access DXA services supported by consultant-guided reporting advice with further follow-up of patients devolved to the primary care setting. An audit was undertaken to assess the number of long-term bisphosphonate users in a GP setting who may be appropriate for a medication review as suggested in the recent NOGG guidance<sup>2</sup>.

### METHOD

Ty Bryn Surgery in Caerphilly was selected for this pilot. GP Egton Medical Information Systems (EMIS) software was employed. The system was interrogated to identify the total number of patients receiving bisphosphonates on repeat prescription, the length of existing therapy and diagnostic code ('osteoporosis'/'osteopenia'). Osteoporotic patients having received > five years of bisphosphonate therapy were identified and a notes review undertaken to collect demographic details for NOGG assessment. These patients were mapped via the NOGG advice to one of four potential outcomes (discontinue, reassess via DXA, re-evaluate or continue bisphosphonate).

### RESULTS

From a GP population of 10,217, 174 patients receiving therapy for BMD were identified. Of these, 102 had a diagnosis of osteoporosis and 60 osteopenia. Due to time limitations, this audit focussed on the former group.

Of 102 patients receiving treatment for osteoporosis, 45 patients were identified as long-term (> five years) users and subject to notes review. Forty-one of these patients were female with a mean age of 73 (range 54–90 years). Treatment (where known) comprised alendronic acid in 29 patients, risedronate in 3 patients, ibandronate in 8 patients and strontium in 2 patients. Mean length of bisphosphonate treatment where known (n = 40) was 9.9 years (range 5–16 years).

Of the 43 patients, 21 had suffered a low trauma fracture (hip fracture n = 4 and vertebral fracture n = 4 patients). Ten patients had received oral steroid therapy (4 current; 6 previous) and 3 patients had rheumatoid arthritis. Reliable pre-treatment DXA results were not available in 17 patients. Fifteen patients had confirmed osteoporotic pre-treatment T scores at lumbar spine and 17 patients at either hip.

A total of 40 patients had sufficient information available in their written notes to complete a NOGG assessment<sup>2</sup>. The two patients who had received strontium treatment were not reviewed in this process. Outcomes in the remaining 38 patients supported a clinical decision to continue (17 patients), discontinue (13 patients), further re-evaluation by specialist (4 patients) or reassess via DXA (4 patients).

### SUMMARY

This pilot of a single Welsh GP population suggests a significant number of patients can be identified on long-term bisphosphonate therapy in primary care. The application of NOGG guidance to this cohort suggests that of the 38 patients reviewed a significant number of patients (55%) should be considered for a medication review or reassessment of the need for continuing therapy to reduce the incidence of uncommon but significant side effects associated with longer-term bisphosphonate use in Wales.



### APPENDIX 3. INFORMATION FOR PATIENTS – SUMMARY OF COCHRANE REVIEW ON ALENDRONATE

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#### **Alendronate for preventing fractures caused by osteoporosis in postmenopausal women**

This summary of a Cochrane review presents what we know from research about the effect of alendronate for preventing fractures (broken bones) caused by osteoporosis.

#### **In women who have already been diagnosed with low bone density, putting them at risk of a fracture, or have already had a fracture in the bones of their spine, alendronate:**

- may prevent fractures in the spine, hip or wrist, or in bones other than the spine.

#### **In women whose bone density is closer to normal, or who may not yet have had a fracture in the bones of their spine, alendronate:**

- probably prevents fractures in the spine
- probably leads to no difference in fractures of the hip, wrist or bones other than the spine.

Possible side effects may include digestive problems such as injury to the throat, oesophagus and stomach and, less commonly, reduced blood supply to the jaw bone, which causes the bone tissue to break down.

#### **What is osteoporosis and what is alendronate?**

Bone is a living, growing part of your body. Throughout your lifetime, new bone cells grow and old bone cells break down to make room for the new, stronger bone. When you have osteoporosis, the old bone breaks down faster than the new bone can replace it. As this happens, the bones lose minerals (such as calcium). This makes bones weaker and more likely to break even after a minor injury, like a little bump or fall. Women are more likely to get osteoporosis after menopause.

Alendronate belongs to the class of drugs called bisphosphonates. It is a type of medication that slows down the cells that break down the old bone.

#### **The best estimate of what happens to women that have already been diagnosed with low bone density or have already had a fracture in the bones of their spine:**

- Fracture of the spine
  - 12 out of 100 women had a fracture when taking a placebo
  - 6 out of 100 women had a fracture when taking alendronate
- Fracture in the hip or wrist
  - 2 out of 100 women had a fracture when taking a placebo
  - 1 out of 100 women had a fracture when taking alendronate
- Fractures in bones other than the spine
  - 9 out of 100 women had a fracture when taking a placebo
  - 7 out of 100 women had a fracture when taking alendronate

#### **The best estimate of what happens to women whose bone density is closer to normal or who may not yet have had a fracture in the bones of their spine:**

- Fracture of the spine
  - 3 out of 100 women had a fracture when taking a placebo
  - 1 out of 100 women had a fracture when taking alendronate
- Fractures in bones other than the spine
  - 1 out of 100 women had a hip fracture when taking a placebo
  - 1 out of 100 women had a hip fracture when taking alendronate
  - 3 out of 100 women had a wrist fracture when taking a placebo
  - 4 out of 100 women had a wrist fracture when taking alendronate
  - 13 out of 100 women had a fracture somewhere other than the spine when taking a placebo
  - 12 out of 100 women had a fracture somewhere other than the spine when taking alendronate<sup>20</sup>.

## APPENDIX 4. SAMPLE PATIENT INFORMATION LEAFLET ON BISPHOSPHONATE DRUG HOLIDAYS

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The below patient information leaflet is provided courtesy of The Newcastle upon Tyne Hospitals NHS, and can be adapted for local use.

### **Bisphosphonates – ‘Drug holidays’ after long-term treatment**

#### **Introduction**

Bisphosphonates are medicines that are used to reduce the risk of fractures in people who have osteoporosis. There are a number of bisphosphonates available in the UK; they include alendronic acid, risedronate and ibandronic acid. If you have been taking a bisphosphonate for a number of years, your healthcare professional (doctor, pharmacist or nurse) may decide to review this treatment and recommend that you stop treatment and have a ‘drug holiday’.

This leaflet explains why you need to have your treatment reviewed, what a drug holiday is and why some patients may need one.

#### **How do bisphosphonates work?**

Bones are constantly being worn away and rebuilt by bone cells. Bisphosphonates slow down the rate that bones are worn away and allow the bone building cells to work more effectively. This increases the density of the bones and reduces the risk of having a fracture.

#### **Why am I taking an oral bisphosphonate?**

These medications are commonly used for people who are at higher risk of having a fracture.

#### **What is a ‘drug holiday’ and why is it necessary?**

A ‘drug holiday’ means you will stop treatment for a period of time, usually up to two years. After this period the need for further treatment is reviewed. Drug holidays are offered to reduce the risk of unusual or ‘atypical’ fractures of the thigh bone (very rare). Unusual or ‘atypical’ fractures of the thigh bone are thought to be more likely to happen in people who have been taking a bisphosphonate for a long period of time. Although bisphosphonates build up bone density (by reducing the amount of bone loss), sustaining this effect for too long could mean that the bone may become more brittle and therefore fracture more easily.

There is good evidence from clinical research to suggest that treatment with bisphosphonates for five years is beneficial and, by increasing the density of bones, they reduce fracture risk.

There are not many data from clinical research that go beyond ten years of treatment. As bisphosphonates may be associated with this very rare side-effect with longer-term treatment, a drug holiday is recommended as a precautionary measure to reduce this risk.

#### **Do I need a drug holiday?**

The decision to stop a bisphosphonate is made on an individual basis. Your healthcare professional will take into account the available evidence and your personal risk factors. For some people treatment may continue for a further year or two. For others treatment may be stopped or changed.

The treatment of osteoporosis has changed over the years as more evidence and research has become available. If the decision is made to stop treatment, your

healthcare professional will discuss the reasons for this with you, including the potential risks and benefits of remaining on treatment.

**What happens after the drug holiday period is over?**

In general, when the drug holiday is over you will be reviewed to assess the need for treatment. The decision to start more treatment is based on the assessment made by your healthcare professional.

The drug holiday period will generally be about two years. You should make sure you meet with your doctor after two years to discuss whether you need a review.

**If I stop treatment will my fracture risk increase?**

If you have taken a bisphosphonate for a number of years, the beneficial effects of treatment are usually maintained for up to three years after your medication is stopped. You will be reviewed during this period of time and the need for any further treatment will be discussed with you.

In some cases a blood test may be taken a few months after stopping treatment to check that the bone is not wearing away too quickly. This is only needed if your risk of fracture is very high before stopping treatment and many people will not need this test. If the blood test shows that bone is wearing away faster than expected, your healthcare professional may decide that you should restart treatment, or change to a different treatment.

**Is this anything to do with NHS cuts?**

No, the advice to stop treatment or to take a drug holiday is a clinical decision, which takes into account the potential risks and benefits. Your healthcare professional will base this decision on what is best for you.

**Where can I find further information?**

If you would like any further information about osteoporosis treatment or you have any concerns about your treatment, you should discuss this with your healthcare professional when you come for your appointment. If you have any queries between appointment times you can contact:

***The National Osteoporosis Society***

Helpline: 0176 147 2721

General enquiries: 0176 147 1771

Web: [www.nos.org.uk](http://www.nos.org.uk)

Address: The National Osteoporosis Society, Camerton, Bath, BA2 0PJ