UKMi
UK Medicines Information
MIDLANDS

TRENT MEDICINES INFORMATION SERVICE

QIPP Detail Aid Support Document

Providing support for quality in prescribing

BISPHOSPHONATES- is a holiday necessary?

KEY MESSAGES

- **Long-term bisphosphonate use has been associated with atypical femoral fractures. The suggestion of stopping therapy or a drug 'holiday' after 5 years treatment has been made in the literature.**
- **National guidance is not available on whether a drug holiday is required, which patients would be suitable or for how long the holiday should be.**
- **The absolute risk of femoral fractures due to bisphosphonates is far lower than the number of osteoporotic fractures prevented.**
- **Some areas have local guidance which should be followed. Otherwise, the following is suggested, after a full discussion of the risks and benefits with the patient.**
- **Patients at continued high risk of an osteoporotic fracture should continue therapy with bisphosphonate. Re-assess at regular intervals and advise patients to report any thigh, hip or groin pain which may be indicative of an atypical femoral fracture. Some local guidance suggests stopping therapy in all patients after 10 years of treatment.**
- **Patients at moderate risk could consider a drug holiday after 5 years of alendronate or 3-5 years of zoledronic acid after discussion. There is limited information about risedronate and no information about ibandronate and drug holidays. Patients should be assessed regularly (at least annually) using tools such as bone markers (eg P1NP) or the FRAX® online tool. Consider restarting therapy after 1-3 years. Alternative non-bisphosphonate therapies may also be an option.**
- **Patients at low risk – consider discontinuing therapy. Re-start when indications for therapy are met.**
- **Ensure adequate intake of calcium and vitamin D in all patients including those who discontinue bisphosphonates.**

WHAT IS THE PROBLEM?

Bisphosphonates such as alendronate or risedronate have become the mainstay of treatment and prevention of osteoporosis, particularly since the use of HRT has declined.

Their long-term use has been associated with several problems, including osteonecrosis of the jaw and atypical femoral fractures. The suggestion of stopping therapy or a drug 'holiday' after 5 years treatment has been made in the literature.

WHAT IS THE EVIDENCE?

In 2011, the MHRA warned of the risk of atypical femoral fractures with bisphosphonates, particularly after long-term use. All bisphosphonates' Summaries of Product Characteristics (SPCs) now contain the advice that 'the optimal 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 on an individual patient basis, particularly after 5 or more years of use.'

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. In 2011, a further Europe-wide review was completed[1]. The key findings were:

- 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 remains favourable. The absolute number of atypical fractures reported is far lower than the number of osteoporotic fractures prevented
- 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

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- 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 absolute number of atypical fractures reported is far lower than the number of osteoporotic fractures prevented. Best available data suggest that, if 150 patients were treated for 8 years with a bisphosphonate, depending on severity of disease, 6-50 vertebral and 6-21 non-vertebral fractures would be prevented; 0.1-1.0 femoral fractures and 0.0015-0.15 cases of osteonecrosis of the jaw may occur.

Depending on the severity of osteoporosis, between 9 and 60 patients need to be treated for 3 years to prevent one vertebral fracture; between 20 and 68 patients need to be treated for 3 years to avoid one non-vertebral fracture. Even discounting the increased risk of fracture with advancing age, the number needed to treat for 8 years would be between 3 and 23 to prevent a vertebral fracture and between 7 and 26 for non-vertebral fracture[2].
Based on the range of risk estimates for osteonecrosis of the jaw, one case would occur for every 1000 to 100,000 patients treated. Using data from California, one atypical femoral fracture would occur in 1282 patients treated for 8 years. Based on Swedish data 8 years of therapy would result in one atypical femoral fracture for every 149 patients treated[2].
These estimates of benefits and risks come from studies generally involving healthy older Caucasian postmenopausal women with osteoporosis and may not pertain to other patients including younger women, men, other races, patients at low fracture risk, and those with other medical problems or who take medications such as glucocorticoids or chemotherapy.

The suggestion of a 'holiday' from bisphosphonate therapy has been made, based on the risks of long term therapy and the fact that bisphosphonate remain in the bone for up to several years after therapy is stopped.

Bisphosphonates have a long half-life in bone and probably continue to be effective for some time after they are withdrawn. Skeletal binding affinity increases in rank order through risedronate, ibandronate, alendronate and zoledronic acid. Bisphosphonates with higher affinity are more quickly re-bound, increasing skeletal retention[2].
Three prospective studies have addressed the issue of efficacy of bisphosphonates after withdrawal of therapy[2-4].
In patients treated with annual zoledronic acid for 3 years, treatment for 3 additional years resulted in a 52% lower risk of morphometric vertebral fracture, compared with treatment for 3 years followed by placebo for the next 3 years (fracture rates 3.0% vs 6.2%, respectively). The risks of other fractures, including clinical or symptomatic vertebral fractures did not differ between groups.
The Fracture Intervention Trial Long-term Extension trial randomized patients completing 5 years of alendronate therapy to 5 additional years of alendronate or placebo. Although the subject number was small, those continuing alendronate for 10 years had fewer clinical vertebral fractures than the subjects receiving the drug for only 5 years (5.3% vs 2.4%. respectively). There was no difference between groups for morphometric vertebral or non-vertebral fractures. A post hoc analysis of the trial patients at high risk *(T* score of < -2.5. but without prevalent vertebral fracture) at the time of discontinuation demonstrated an increased risk for all clinical fractures associated with a discontinuation compared with remaining on alendronate therapy.
In a small study of patients given risedronate or placebo for 3 years who were then followed for an additional year after discontinuation, morphometric vertebral fracture incidence remained 46% lower in the former risedronate group, as compared with the former placebo group (6.5% vs 11.6%. respectively). However. there was no group of patients continuing on risedronate so it was not possible to compare fracture risk of discontinuing therapy with continuing therapy. Increased risk of fracture upon discontinuing bisphosphonates compared with continuing therapy also has been observed in analyses of large health care databases.
One author has proposed that discontinuation should be limited to alendronate and zoledronic acid[4]. This is based on observational studies showing greater bone loss after discontinuation of risedronate therapy and lack of data for ibandronate. This corresponds with the data that alendronate and zoledronic acid have greater skeletal binding than other bisphosphonates[2].

No clear UK guidelines are available advising whether a drug holiday is required, which patients would be suitable or how long the holiday should be for.

As discussed above, the MHRA have stated that 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[1].
In 2011, the FDA conducted a review of long-term bisphosphonates to assess their safety and whether there should be a recommended 'drug holiday' or maximum duration of therapy. The outcome was to increase the cautionary language on the product labels; they did not go as far as recommending limiting use of the drugs to five years. The panel commented that the data are not sufficient to allow estimation of the balance of risks and benefits of taking these medicines for longer than three to five years, and to therefore make any specific recommendations on a maximum duration of therapy[3].
The Royal College of General Practitioners, in association with the National Osteoporosis Society, have produced a question and answer document[5]. This suggests that oral bisphosphonates treatment is usually given for five years in the first instance. If bone mineral density (BMD) remains the same or has improved from baseline, the post-treatment T-

score is > −2.5 and no fractures have occurred during treatment, it may be reasonable to withdraw bisphosphonate treatment for two to three years with reassessment of fracture risk at the end of that time and re-continuation of treatment if indicated. Because the effects of intravenous zoledronic acid last for longer than oral bisphosphonates, a drug holiday should be considered after three rather than five years of treatment.

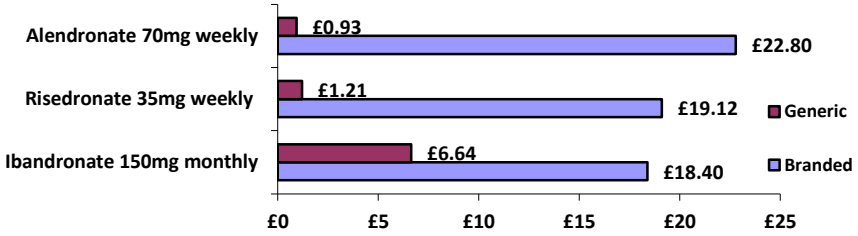
In the absence of clear guidance US specialists have suggested patients still at high risk of osteoporotic fracture should continue therapy with bisphosphonate. Patients should be re-assessed at regular Intervals for the need for continued therapy and advised to report any thigh, hip or groin pain which may indicate an atypical fracture. Those at moderate risk should consider a drug holiday after 3-5 years of therapy after informed discussion. Data on duration of holiday are not available but reassessment after 2 years has been suggested. Those at low risk could discontinue therapy; re-start when indications for therapy are met.

There have been some opinions suggested in the US literature[2-4] that:

- Patients with low BMD at the femoral neck (T score < −2.5) after 3 to 5 years of treatment are at the highest risk for vertebral fractures and therefore are likely to benefit most from continuation of bisphosphonates.
- Patients with an existing vertebral fracture who have a somewhat higher (although not > −2.0) T score for BMD may also benefit from continued therapy.
- Patients with a femoral neck T score > −2.0 have a low risk of vertebral fracture and are unlikely to benefit from continued treatment.

Several UK health communities have produced local guidance. All agree that a drug holiday or maximum duration of therapy is appropriate but there is little consensus on duration of therapy before taking a holiday, duration of drug holiday or how to monitor patients either during the holiday or when considering restarting therapy.
Some local guidelines emphasise the importance of continued monitoring of patients either by on-going DEXA scan to measure BMD, measuring bone turnover markers such as P1NP (type 1 procollagen amino-terminal-propeptide) or using an online tool, such as FRAX[6], a tool developed by the WHO to evaluate fracture risk of patients.

WHAT ARE THE COSTS?



Costs for 28 days supply. Taken from MIMS/ Drug Tariff July 2013

Most bisphosphonates have come off patent in recent years. Branded prescribing still occurs; for risedronate 5% of prescriptions are for the branded product but these make up 37% of the cost. £180,000 could have been saved in 2012-13 in the East Midlands purely by generic prescribing of bisphosphonates.

Risedronate came off patent in 2011, ibandronate in 2012. The availability of generic products has dramatically reduced the cost of bisphosphonate prescribing and these savings are beginning to be realised.

EAST MIDLANDS	**Total Items**			**Total Act Cost**	
	Financial year 2011/2012	Financial year 2012/2013		Financial year 2011/2012	Financial year 2012/2013
Alendronic Acid	577,570	609,634		£685,098.72	£604,006.93
Fosamax	3,790	2,651		£93,940.77	£67,875.77
Alendronic Acid & Colecalciferol	3,029	2,519		£76,110.14	£61,856.95
Risedronate	60,437	56,922		£397,373.19	£80,240.68
Actonel	4,229	3,166		£82,809.89	£63,087.49
Ibandronic Acid 150mg tablets	22,469	19,137		£501,047.14	£419,017.38
Bonviva Tablets 150mg	4,439	3,461		£97,812.75	£77,476.78

References:

1. MHRA Drug Safety Update June 2011, vol 4, issue 4: (http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON120213)
2. Am J Med (2013) 126, 13-20
3. Whitaker M, Guo J, Kehoe T et al Bisphosphonates for Osteoporosis — Where Do We Go from Here? N Engl J Med 2012; 366: 2048-2051
4. Black DM, Bauer DC, Schwartz AV et al Continuing Bisphosphonate Treatment for Osteoporosis —For Whom and for How Long? N Engl J Med 2012; 366: 2051-3
5. Royal College of General Practitioners and the National Osteoporosis Society. Duration of treatment http://www.osteoporosis-resources.org.uk/implementation/22-duration-of-treatment
6. http://www.shef.ac.uk/FRAX/

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