# SDCEP logoNHS Education for Scotland logo

# Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw

## Dental Clinical Guidance

## March 2017

Reviewed and extant March 2024  
Please [refer to supplement](https://www.sdcep.org.uk/published-guidance/medication-related-osteonecrosis-of-the-jaw/)

### This guidance is an update to the 2011 SDCEP publication Oral Health Management of Patients Prescribed Bisphosphonates

# 

©Scottish Dental Clinical Effectiveness Programme

SDCEP operates within NHS Education for Scotland. You may copy or reproduce the information in this document for use within NHSScotland and for non-commercial educational purposes.

Use of this document for commercial purposes is not permitted.

ISBN 978 1 905829 29 3

First published 2017

Scottish Dental Clinical Effectiveness Programme

Dundee Dental Education Centre, Frankland Building, Small’s Wynd, Dundee DD1 4HN

Emailscottishdental.cep@nes.scot.nhs.uk

Tel01382 425751 / 425771

Websitewww.sdcep.org.uk

## Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw

[Summary of Key Recommendations 3](#_Toc473624682)

[1. Introduction 7](#_Toc473624683)

[1.1 Scope of This Guidance 7](#_Toc473624684)

[1.2 Development and Presentation of the Guidance Recommendations 8](#_Toc473624685)

[1.3 Supporting Tools 9](#_Toc473624686)

[1.4 Statement of Intent 9](#_Toc473624687)

[2. Medication-related Osteonecrosis of the Jaw (MRONJ) 10](#_Toc473624688)

[2.1 What is MRONJ? 10](#_Toc473624689)

[2.2 What Are Anti-resorptive Drugs and How Do They Work? 12](#_Toc473624690)

[2.3 What Are Anti-angiogenic Drugs and How Do They Work? 13](#_Toc473624691)

[2.4 Treatment of MRONJ 14](#_Toc473624692)

[2.5 MRONJ in Children 14](#_Toc473624693)

[2.6 Adverse Drug Reaction Reporting 14](#_Toc473624694)

[3. Classification of Patient Risk 16](#_Toc473624695)

[3.1 Risk Factors 16](#_Toc473624696)

[3.2 Assessing Patient Risk 19](#_Toc473624697)

[4. Managing Patients at Risk of Medication-related Osteonecrosis of the Jaw (MRONJ) 25](#_Toc473624698)

[4.1 Initial Management of Patients at Risk of MRONJ 26](#_Toc473624699)

[4.2 Continuing Management of Patients at Risk of MRONJ 28](#_Toc473624700)

[5. Research and Audit 31](#_Toc473624701)

[5.1 Recommendations for Research 31](#_Toc473624702)

[5.2 Recommendations for Audit 31](#_Toc473624703)

[Appendix 1 Guidance Development 32](#_Toc473624704)

[The Programme Development Team 32](#_Toc473624705)

[The Guidance Development Group 34](#_Toc473624706)

[Guidance Development Methodology 35](#_Toc473624707)

[Review and Updating 37](#_Toc473624708)

[Steering Group 37](#_Toc473624709)

[Conflict of Interest 37](#_Toc473624710)

[Appendix 2 Drugs Associated with MRONJ Prescribed in the United Kingdom 38](#_Toc473624711)

[Appendix 3 Managing the Oral Health of Patients at Risk of MRONJ 40](#_Toc473624712)

[Appendix 4 Points to Cover During MRONJ Risk Discussion 41](#_Toc473624714)

[Appendix 5 Guidance for Prescribers and Dispensers of Anti-resorptive or Anti-angiogenic Drugs 46](#_Toc473624715)

[Appendix 6 Patient Information 47](#_Toc473624716)

[References 48](#_Toc473624717)

## Summary of Key Recommendations

This summary lists the key recommendations and abbreviated versions of the advice provided within the guidance. The summary is not comprehensive and for a full appreciation of the recommendations, the basis for making them, and other points for consideration, it is necessary to read the whole guidance.

### Classification of Patient Risk [Refer to Section 3]

Assess whether a patient taking anti-resorptive or anti-angiogenic drugs is at low risk or higher risk of developing MRONJ based on their medical condition, type and duration of drug therapy and any other complicating factors and record this in the patient’s clinical notes.

* Ask about past, current, or possible future use of anti-resorptive or anti-angiogenic drugs when taking or confirming a medical history.
* Assign a level of risk based on an assessment of the medical condition that the patient is being treated for and any other complicating factors such as concurrent glucocorticoid medication and length of exposure to the drugs. See Table 3.1 and Figure 3.1 for further information.
* Ensure that the assigned risk level is recorded in the patient’s clinical record.
* Be aware that any low risk patient who continues to take bisphosphonate drugs after their five-year medication review should be reclassified as higher risk.
* If a patient has taken anti-resorptive drugs in the past but is no longer taking them for whatever reason (i.e. completed or discontinued the course or taking a drug holiday), allocate them to a risk group as follows:
* If a patient has taken bisphosphonates in the past, allocate them to a risk group as if they are still taking the drugs.
* If a patient has taken denosumab in the past nine months, allocate them to a risk group as if they are still taking the drug.

N.B. Patients who have previously taken anti-angiogenic drugs in combination with anti-resorptive drugs should be allocated to a risk group based on their history of anti-resorptive drug use.

### Initial Management of Patients at Risk of MRONJ [Refer to Section 4]

Before commencement of anti-resorptive or anti-angiogenic drug therapy, or as soon as possible thereafter, aim to get the patient as dentally fit as feasible, prioritising preventive care. Higher risk cancer patients should preferably undergo a thorough dental assessment, with remedial dental treatment where required, prior to commencement of the drug therapy.

* Advise the patient (or carer, where appropriate) that, due to the medication they are taking, there may be a risk of developing MRONJ but ensure that they understand that the risk is small. It is very important that a patient is not discouraged from taking their anti-resorptive or anti-angiogenic medication or from undergoing dental treatment. Record that this advice has been given.
* Give personalised preventive advice to help the patient optimise their oral health.
* Prioritise care that will reduce mucosal trauma or may help avoid future extractions or any oral surgery or procedures that may impact on bone.
* For medically complex patients for whom you would normally seek advice, including higher risk patients who are being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer, consider consulting an oral surgery/special care dentistry specialist with regards to clinical assessment and treatment planning.

### Continuing Management of Patients at Risk of MRONJ [Refer to Section 4]

Carry out all routine dental treatment as normal and continue to provide personalised preventive advice in primary care. Perform straightforward extractions and other bone-impacting treatments in low risk patients in primary care. Adopt a more conservative approach in higher risk patients, giving greater consideration to other, less invasive alternative treatment options before performing extractions and other bone-impacting treatments in primary care.

Do not prescribe antibiotic or antiseptic prophylaxis following extractions or other bone-impacting treatments specifically to reduce the risk of MRONJ.

**Low Risk Patients**

Having made the patient as dentally fit as feasible:

* Carry out all routine dental treatment as normal and continue to provide personalised preventive advice.
* If an extraction or another procedure that impacts on bone is required:
  + Discuss the risks and benefits associated with treatment with the patient (or carer, where appropriate) to ensure valid consent and proceed with the treatment as clinically indicated;
  + Do not prescribe antibiotic or antiseptic prophylaxis unless required for other clinical reasons;
  + Advise the patient to contact the practice if they have any concerns, such as unexpected pain, tingling, numbness, altered sensation or swelling in the extraction area;
  + Review healing. If the extraction socket is not healed at **8 weeks** and you suspect that the patient has MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.
* If you suspect a patient has spontaneous MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.
* Consider reporting any suspected case of MRONJ to the MHRA via the yellow card scheme ([www.yellowcard.mhra.gov.uk](http://www.yellowcard.mhra.gov.uk)) and encourage the patient to do likewise.

**Higher Risk Patients**

Having made the patient as dentally fit as feasible:

* Carry out most routine dental treatment as normal and continue to provide personalised preventive advice.
* For medically complex patients for whom you would normally seek advice, including higher risk patients who are being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer, consider consulting an oral surgery/special care dentistry specialist with regards to clinical assessment and treatment planning.
* If an extraction is indicated, explore all possible alternatives where teeth could potentially be retained e.g. retaining roots in absence of infection.
* If extraction remains the most appropriate treatment:
  + Discuss the risks and benefits associated with treatment with the patient (or carer, where appropriate) to ensure valid consent and proceed with the treatment as clinically indicated;
  + Do not prescribe antibiotic or antiseptic prophylaxis unless required for other clinical reasons;
  + Advise the patient to contact the practice if they have any concerns, such as unexpected pain, tingling, numbness, altered sensation or swelling in the extraction area;
  + Review healing. If the extraction socket is not healed at 8 weeks, and you suspect that the patient has MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.
* If you suspect a patient has spontaneous MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.
* Consider reporting any suspected case of MRONJ to the MHRA via the yellow card scheme ([www.yellowcard.mhra.gov.uk](http://www.yellowcard.mhra.gov.uk)) and encourage the patient to do likewise.

# 1. Introduction

Patients who are taking anti-resorptive or anti-angiogenic drugs have a small risk of developing medication-related osteonecrosis of the jaw (MRONJ). This condition may be more prevalent in patients who have dental procedures which impact on bone, for example extractions.

This guidance has been developed to support dental practitioners to manage the routine dental treatment of patients prescribed drugs associated with osteonecrosis of the jaw. These include anti-resorptive drugs, such as the bisphosphonates and denosumab, and anti-angiogenic therapies, such as bevacizumab, sunitinib and aflibercept. Prescribers and dispensers of these drugs, as well as patients and their carers, where appropriate, may also find the information in this guidance of relevance.

## 1.1 Scope of This Guidance

Dental practitioners are likely to see patients who are taking anti-resorptive or anti-angiogenic drugs in primary care as these drugs are prescribed to prevent, as well as to treat, a wide variety of medical conditions. This guidance aims to help minimise the risk of medication-related osteonecrosis of the jaw (MRONJ) developing in these patients and to encourage a consistent approach to their oral health management. The guidance also aims to empower dental staff to provide routine dental care for this patient group within primary care thereby minimising the need for consultation and referral to secondary care. The specialist management of dental patients with MRONJ lesions is beyond the scope of this guidance and is not discussed.

The guidance is primarily directed at dentists in primary care dental practice, including the general dental service and public dental service, and will also be of relevance to the secondary care dental service, those involved in dental education and undergraduate trainees.

This guidance is an update to the 2011 Scottish Dental Clinical Effectiveness Programme (SDCEP) publication *Oral Health Management of Patients Prescribed Bisphosphonates* and takes into account the wider range of drugs that have been implicated in the development of MRONJ. The recommendations in this guidance have been updated to reflect the most up-to-date evidence and advances in clinical experience with this patient group.

## 1.2 Development and Presentation of the Guidance Recommendations

To develop the recommendations for this guidance, SDCEP convened a multidisciplinary guidance development group including medical and dental practitioners and specialists along with patient representatives (Appendix 1). The key recommendations presented in the guidance were developed through considered judgements, made by the group, based on existing guidelines, the available evidence, clinical experience, expert opinion and patient and practitioner perspectives. Details of these considered judgements are available at [www.sdcep.org.uk](http://www.sdcep.org.uk). The impact of potential barriers identified during guidance development and through stakeholder involvement and external consultation was also considered when formulating the recommendations.

**Strength of recommendations**

The process for the development of recommendations followed the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach (www.gradeworkinggroup.org). The strength of each key recommendation is stated directly after the recommendation with a brief justification in the accompanying text. Strength of recommendation is not automatically dictated by evidence quality. Other factors, such as applicability, consistency and balance of benefits and harms are considered when forming recommendations and it is possible to make a strong recommendation where the evidence base is considered weak. A strong recommendation is one where it is considered, based on all the available information and weighing up the balance of benefits versus risk, that almost all individuals would choose this option. A conditional recommendation is one where there is a finer balance between the options and it is likely that the majority but not all would choose the recommended option. In the case of a conditional recommendation, the practitioner should expect to spend more time discussing the management options so that the patient can make an informed decision. Further details can be found in Appendix 1 and at www.sdcep.org.uk.

Other clinical practice advice in this guidance is based on consensus, expert opinion and existing best practice as identified in the accompanying text.

## 1.3 Supporting Tools

* A list of drugs associated with MRONJ prescribed in the United Kingdom is presented in Appendix 2.
* A guide outlining the management of patients prescribed anti-resorptive or anti-angiogenic drugs is presented in Appendix 3.
* Advice on how to discuss MRONJ risk with patients is presented in Appendix 4.
* Information for prescribers and dispensers of anti-resorptive or anti-angiogenic drugs is presented in Appendix 5.
* General information to provide to patients in the form of a leaflet is presented in Appendix 6.

The following guidance for dental practitioners in primary care is also summarised at the beginning of the document.

## 1.4 Statement of Intent

This guidance is based on careful consideration of the available information and resources at the time of issue and has been developed through consultation with experts and end-users (see Appendix 1). As guidance, it does not override the healthcare professional’s right, and duty, to make decisions appropriate to each patient, with their informed consent. However, it is advised that departures from this guidance, and the reasons for this, are fully documented in the patient’s clinical record.

SDCEP is funded by NES (NHS Education for Scotland). The views and opinions of NES have not in any way influenced the recommendations made in this guidance.

This resource may be made available, in full or summary form, in alternative formats and community languages. Please contact us on 0131 656 3200or email altformats@nes.scot.nhs.ukto discuss how we can best meet your requirements.

# 2. Medication-related Osteonecrosis of the Jaw (MRONJ)

## 2.1 What is MRONJ?

Medication-related osteonecrosis of the jaw (MRONJ) is a rare side effect of anti-resorptive and anti-angiogenic drugs. It is defined as exposed bone, or bone that can be probed through an intraoral or extraoral fistula, in the maxillofacial region that has persisted for more than eight weeks in patients with a history of treatment with anti-resorptive or anti-angiogenic drugs, and where there has been no history of radiation therapy to the jaw or no obvious metastatic disease to the jaws.[1](#_ENREF_1)

Although the majority of cases of MRONJ occur following a dental intervention which impacts on bone, some can occur spontaneously. Signs and symptoms include delayed healing following a dental extraction or other oral surgery, pain, soft tissue infection and swelling, numbness, paraesthesia or exposed bone. Patients may also complain of pain or altered sensation in the absence of exposed bone. However, be aware that some patients may be asymptomatic at presentation, with MRONJ lesions an incidental finding. A history of anti-resorptive or anti-angiogenic drug use in these patients should alert practitioners to the possibility of MRONJ. Appendix 2 presents a list of anti-resorptive and anti-angiogenic drugs currently prescribed in the UK.

At present, the pathophysiology of the disease has not been fully determined and there is much debate about the mechanisms by which these drugs induce necrosis in the jaw bone. Current hypotheses for the causes of necrosis include suppression of bone turnover, inhibition of angiogenesis, toxic effects on soft tissue, inflammation or infection.[1](#_ENREF_1) It is likely that the cause of the disease is multi-factorial, with both genetic and immunological elements. Risk factors include the underlying medical condition for which the patient is being treated, cumulative drug dose (also linked to duration of drug treatment), concurrent treatment with systemic glucocorticoids, dentoalveolar surgery and mucosal trauma.

**MRONJ Incidence in Cancer Patients**   
(Please refer to 2024 supplement for updated incidence information)

MRONJ has been observed in patients being treated with anti-resorptive or anti-angiogenic drugs for management of solid tumour cancers (e.g. breast cancer, prostate cancer) and multiple myeloma and other cancers of the blood. Estimates of incidence and prevalence vary due to the rare nature of MRONJ. In these cancer patients, the MRONJ risk ranges from 0 to 12% (0-1200 cases per 10,000)[2-5](#_ENREF_2) compared to a risk of 0 to 0.02% (0-2 cases per 10,000) in cancer patients exposed to placebo in clinical trials.[1](#_ENREF_1) However, it should be noted that estimates towards the higher end of this range tended to come from studies with small sample sizes which can overestimate the risk of low frequency events. When only considering data from studies with >500 patients, the risk of MRONJ in cancer patients approximates 1% (ranging from 0 to 2.3%).[[1]](#footnote-2)ǂ This agrees with an estimate of MRONJ risk based on studies with Level 1 evidence (systematic reviews or RCTs).[1](#_ENREF_1) However, it should be noted that incidence may vary depending on cancer type and treatment regime, with patients with prostate cancer or multiple myeloma thought to be at increased risk. There are fewer data available to estimate the risk of MRONJ in cancer patients treated with anti-angiogenic drugs. However, one study reports a risk of 0.2% (20 cases per 10,000) in cancer patients treated with bevacizumab.[6](#_ENREF_6) It also appears the risk is increased when anti-angiogenics are used in conjunction with anti-resorptive drugs (both given simultaneously) or are given to those with a history of bisphosphonate use.[1](#_ENREF_1)

**MRONJ Incidence in Osteoporosis Patients**

The risk of MRONJ in patients being treated with oral anti-resorptive drugs for osteoporosis is lower than the risk for patients being treated for cancer. Estimates range from 0 to 0.1% (0-10 cases per 10,000),[1](#_ENREF_1),[2](#_ENREF_2),[5](#_ENREF_5),[7-9](#_ENREF_7) with a recent UK study estimating incidence to be ‘more than 1 in 10,000 and less than 1 in 1000’.[10](#_ENREF_10) Another UK study estimated that the incidence of alendronate-associated osteonecrosis of the jaw in this patient group is 4.3 per 10,000 drug patient years (0.043%).[11](#_ENREF_11) There is some weak evidence that the risk appears to increase with increasing drug duration.[12](#_ENREF_12) The risk of MRONJ in patients with osteoporosis given a once yearly intravenous infusion of bisphosphonates appears to be no greater than that in patients taking the drugs orally, with one study identifying one case of MRONJ in a sample of around 6000 patients (0.017%).[13](#_ENREF_13) There is less evidence to base an estimate of incidence in those patients prescribed denosumab. The Summary of Product Characteristics (SmPC) for Prolia®, the denosumab formulation indicated for treatment of osteoporosis, reports that 13 cases of MRONJ were observed in 4450 patients (0.3%) over seven years of an extended phase III clinical study.[14](#_ENREF_14)

**Table 2.1 Incidence of MRONJ in specific patient groups**(Please refer to 2024 supplement for updated incidence information)

|  |  |
| --- | --- |
| Estimated incidence of MRONJ in cancer patients treated with anti-resorptive or anti-angiogenic drugs | **1%** (1 case per 100) |
| Estimated incidence of MRONJ in osteoporosis patients treated with anti-resorptive drugs | **0.01-0.1%** (1-10 cases per 10,000) |

The figures in Table 2.1 illustrate that MRONJ is a rare condition in the osteoporosis patient group, while the risk in cancer patients is up to 100 times greater. The risk of MRONJ should be discussed with patients but it is important that they are not discouraged from taking anti-resorptive or anti-angiogenic drugs or from undergoing dental treatment.

## 2.2 What Are Anti-resorptive Drugs and How Do They Work?

Bone is constantly being remodelled by the action of osteoblasts, which create bone tissue, and osteoclasts, which break down (resorb) bone tissue. Anti-resorptive drugs inhibit osteoclast differentiation and function, leading to decreased bone resorption and remodelling. The jaw is known to have an increased remodelling rate compared to other skeletal sites and therefore the viability of bone in this region may be adversely affected by the action of these drugs.

There are two main types of anti-resorptive drugs that have been associated with osteonecrosis of the jaw, the bisphosphonates and denosumab. These are used in the management of osteoporosis and other non-malignant and malignant conditions. Anti-resorptive drugs can have a significantly positive effect on the quality of life of patients by reducing or delaying onset of disease or treatment complications, such as bone fractures and bone pain.

**Bisphosphonates**

The bisphosphonates reduce bone resorption by inhibiting enzymes essential to the formation, recruitment and function of osteoclasts. The drugs have a high affinity for hydroxyapatite and persist in the skeletal tissue for a significant period of time, with alendronate having a half-life in bone of around 10 years.[15](#_ENREF_15) However, it is unclear how this influences the risk of MRONJ once a patient has stopped taking the drugs. It is speculated that the bisphosphonates may also have an adverse effect on soft tissue cells by inhibiting proliferation and increasing apoptosis, which may lead to delayed soft tissue healing.[16](#_ENREF_16),[17](#_ENREF_17) There is also some evidence that these drugs can inhibit angiogenesis.[18](#_ENREF_18)

Bisphosphonates are used to reduce the symptoms and complications of metastatic bone disease (particularly that associated with breast cancer, prostate cancer and multiple myeloma). The drugs are usually delivered as regular high dose intravenous infusions in this patient group.

Bisphosphonates are also indicated for the treatment of osteoporosis and other less common disorders of the bone such as Paget’s disease, osteogenesis imperfecta and fibrous dysplasia. They are additionally used as prophylaxis to counteract the osteoporotic effects of glucocorticoids and to prevent bone-related/skeletal complications in patients with primary hyperparathyroidism and cystic fibrosis. Patients in these groups can take the drugs orally (usually once a week) or the drugs can be given as quarterly or yearly infusions.

**Denosumab**

Denosumab is a fully human monoclonal antibody which inhibits osteoclast function and associated bone resorption by binding to the receptor activator nuclear factor κB ligand (RANKL). Like the bisphosphonates, denosumab is indicated for the prophylaxis and treatment of osteoporosis and to reduce skeletal-related events related to metastasis. Denosumab is administered subcutaneously every six months in osteoporosis patients, with a higher dose given monthly in patients with metastatic disease. Denosumab does not bind to bone and its effects on bone turnover diminish within nine months of treatment completion.[14](#_ENREF_14),[19](#_ENREF_19)

## 2.3 What Are Anti-angiogenic Drugs and How Do They Work?

Anti-angiogenic drugs target the processes by which new blood vessels are formed and are used in cancer treatment to restrict tumour vascularisation.

Not all anti-angiogenic drugs are currently implicated in MRONJ. However, thevascular endothelial growth factor (VEGF) inhibitors bevacizumab and aflibercept and the receptor tyrosine kinase (RTK) inhibitor sunitinib have been associated with osteonecrosis of the jaw and the Medicines and Healthcare products Regulatory Agency (MHRA) has issued Drug Safety Updates identifying MRONJ as a possible side effect of these drugs.[20](#_ENREF_20),[21](#_ENREF_21)

Anti-angiogenic drugs can be used in combination with the bisphosphonates in the management of cancer and there is some evidence that this results in a greater MRONJ risk.[6](#_ENREF_6) This may also be true where anti-angiogenic drugs are used in patients with a previous history of bisphosphonate use.

The use of anti-angiogenic drugs in cancer is an expanding field and it is likely that any future medications with these modes of action may also have an associated risk of MRONJ.

## 2.4 Treatment of MRONJ

The treatment of MRONJ is beyond the scope of this guidance as patients with suspected MRONJ should be referred to a specialist. A Cochrane Review[22](#_ENREF_22) published in 2016 investigated the safety and efficacy of interventions for treating bisphosphonate-related osteonecrosis of the jaw. However, the authors found a lack of evidence from randomised controlled trials and concluded that high quality randomised controlled trials are needed.

## 2.5 MRONJ in Children

Bisphosphonates are used in children for the management of osteogenesis imperfecta, fibrous dysplasia, neuromuscular disorders, bone dysplasia, idiopathic juvenile osteoporosis, rheumatologic disorders and Crohn’s disease.[23](#_ENREF_23) The evidence for MRONJ in paediatric patients is scarce, with three review articles stating that there have been no cases of MRONJ reported in the paediatric patient group.[23-25](#_ENREF_23) Children who are prescribed anti-resorptive drugs to manage these medical conditions are likely to be managed by specialists in paediatric dentistry.

## 2.6 Adverse Drug Reaction Reporting

MRONJ is an adverse drug reaction and as such is monitored by the Medicines and Healthcare products Regulatory Agency (MHRA; [www.mhra.gov.uk](http://www.mhra.gov.uk)). If a patient has suspected MRONJ, dental practitioners are encouraged to notify the MHRA via the Yellow Card Scheme ([www.yellowcard.mhra.gov.uk](http://www.yellowcard.mhra.gov.uk)). Reporting is important to help the MHRA assess additional risk factors and identify drugs not previously associated with MRONJ. Duplicate reporting, for example by clinicians in both primary and secondary care, does not lead to over-estimation of incidence as duplicate reports are identified and can add value to the overall information on a suspected adverse drug reaction. Reporting is confidential and patients should also be encouraged to report via the scheme.

# 3. Classification of Patient Risk

There are some factors that may increase MRONJ risk and so influence the dental management options for a patient on anti-resorptive or anti-angiogenic drugs (or who have taken one of these drugs in the past). Despite this, the majority of patients are able to receive all their dental treatment in primary care, with referral only appropriate for those with delayed healing.

## 3.1 Risk Factors

The most significant risk factor for MRONJ is the underlying medical condition for which the patient is being treated, with patients being treated for cancer considered at higher risk than those being treated for osteoporosis. Patients who have had a previous episode of MRONJ, irrespective of their underlying medical condition, are also considered as being at higher risk.

**Dental Treatment**

Dentoalveolar surgery, or any other procedure that impacts on bone, is considered a risk factor for MRONJ, with tooth extraction a common precipitating event. However, it is important to acknowledge that MRONJ is an adverse effect of treatment with anti-resorptive or anti-angiogenic drugs and although invasive dental treatment is a risk factor, it does not cause the disease. Dental trauma, including mucosal trauma from ill-fitting dentures or other appliances, is also considered a risk factor. There is some evidence that dental infection and untreated periodontal disease may increase the risk of MRONJ.[26](#_ENREF_26),[27](#_ENREF_27) This may reflect that a common treatment of these dental diseases is tooth extraction. A recent systematic review[28](#_ENREF_28) estimates that the incidence of MRONJ after tooth extraction is 2.9% in patients with cancer and 0.15% in patients being treated for osteoporosis, with a recent tooth extraction observed in around 60% of patients who develop MRONJ.[29-32](#_ENREF_29) However, MRONJ can occur ‘spontaneously’ without the patient having undergone any recent invasive dental treatment.

**Duration of Bisphosphonate Drug Therapy**

The risk of MRONJ in patients being treated with bisphosphonate drugs is thought to increase as the cumulative dose of the drug increases, as a consequence of the long half-life of this drug class. This may explain the increased MRONJ risk in patients being treated with high dose bisphosphonate drugs for the management of cancer compared to those being treated with the lower dose, mostly oral drugs for the management of osteoporosis or other non-malignant diseases of the bone. However, even in this lower risk patient group, the MRONJ risk may be influenced by the length of time that a patient has been exposed to the drug, with one study finding a higher prevalence of MRONJ in patients who had taken oral bisphosphonates for more than four years compared to those who had taken the drugs for less than this time period.[12](#_ENREF_12)

**Other Concurrent Medication**

Chronic systemic glucocorticoid use has been reported in some studies to increase the risk for MRONJ when taken in combination with anti-resorptive drugs.[30](#_ENREF_30),[33-36](#_ENREF_33) However, the association has not been observed in other studies.[37-39](#_ENREF_37) The combination of bisphosphonates and anti-angiogenic agents has also been associated with increased risk of MRONJ.[6](#_ENREF_6),[30](#_ENREF_30) The risk appears to be increased if the drugs are taken concurrently or if there has been a history of bisphosphonate use.[6](#_ENREF_6),[30](#_ENREF_30)

**Dental Implants**

The risk of MRONJ following the placement of dental implants in patients being treated with anti-resorptive or anti-angiogenic drugs is currently unknown.[1](#_ENREF_1) It is generally agreed that implant placement should be avoided in patients who are being treated with high dose anti-resorptive or anti-angiogenic drugs for the management of cancer.[1](#_ENREF_1),[2](#_ENREF_2)

Implant placement is not currently contraindicated in patients with osteoporosis. At present, there is insufficient evidence to indicate whether bisphosphonates have a negative impact on implant survival in terms of osseointegration[40-45](#_ENREF_40) and failure rates appear similar to those in patients with no history of bisphosphonate use. However, there are reports of MRONJ in patients with dental implants.[39](#_ENREF_39),[41](#_ENREF_41),[46-51](#_ENREF_46) The overall risk in this patient group appears to be low and reports of MRONJ are less frequent in patients whose dental implants were placed before bisphosphonate drug treatment commenced. For patients who have implants placed during or after bisphosphonate drug treatment, MRONJ has been observed both shortly after implant placement or a significant time after the procedure. There is no data on implant survival in patients treated with denosumab.

* Inform patients with dental implants placed prior to commencement with anti-resorptive or anti-angiogenic drugs, of the small risk of spontaneous MRONJ at those sites and provide information on how to minimise their risk, for example ensuring excellent oral hygiene at implant site(s).
* Inform osteoporosis patients who consider dental implants during or after treatment with anti-resorptive drugs of the risk of compromised bone healing and MRONJ following the procedure and the additional small risk of long-term implant failure. Provide information for those patients who choose to go ahead with the procedure on how to minimise their risk, for example ensuring excellent oral hygiene at implant site(s).

**Drug holidays**

There is no evidence that MRONJ risk will be reduced if the patient temporarily, or even permanently, stops taking bisphosphonate drugs prior to invasive dental procedures since the drugs may persist in the skeletal tissue for years. The decision to initiate a drug holiday is the responsibility of the prescribing physician and dental practitioners should not discourage patients from continuing with their medication.

Although not strictly a drug holiday, an acceptable management option for patients with osteoporosis who are being treated with six monthly subcutaneous injections of denosumab is to delay any non-urgent invasive dental treatment in an asymptomatic tooth until the month prior to the patient’s next scheduled drug administration. Resumption of denosumab treatment following invasive dental treatment should be delayed until the soft tissues/extraction socket have healed. It will therefore be necessary to closely liaise with the patient’s medical practitioner to successfully coordinate this management option.

**Previous Treatment with Anti-resorptive or Anti-angiogenic Drugs**

There is currently no evidence to inform the assessment of risk for patients who have previously taken anti-resorptive or anti-angiogenic drugs.

Bisphosphonates are known to remain in the body for a significant amount of time after the patient stops taking them. Therefore, if a patient has taken bisphosphonate drugs in the past but is no longer taking them for whatever reason (i.e. completed or discontinued the course or taking a drug holiday), they should be allocated to a risk group as if they are still taking the drugs.

The effect of denosumab on bone turnover diminishes within nine months of treatment completion.[14](#_ENREF_14),[19](#_ENREF_19)

Anti-angiogenic drugs are not thought to remain in the body for extended periods of time.

## 3.2 Assessing Patient Risk

**KEY RECOMMENDATION:**

Assess whether a patient taking anti-resorptive or anti-angiogenic drugs is at low risk or higher risk of developing MRONJ based on their medical condition, type and duration of drug therapy and any other complicating factors and record this in the patient’s clinical notes.

(Strong recommendation; low quality evidence)

While the overall risk of MRONJ is small, some patient groups have a higher risk than others and this may impact their subsequent oral health management. An up-to-date medical history is essential in identifying those patients who are, or have been, exposed to anti-resorptive or anti-angiogenic drugs and to identify any additional risk factors, such as chronic use of systemic glucocorticoids. Communication with the patient’s GMP may be required to obtain more information about the patient’s medical condition and drug regimen(s).

**Patients being treated for cancer**

Patients being treated with anti-resorptive or anti-angiogenic drugs (or both) as part of the management of cancer are always considered to be at higher risk of MRONJ.

**Patients being treated for osteoporosis or other non-malignant diseases of bone**

The assessment of these patients is more complicated; the risk for each patient will depend on a combination of factors and should be assessed on the basis of patient-specific information. An up-to-date medical history is essential in identifying those patients who are, or have been, exposed to anti-resorptive drugs and to identify any additional risk factors, such as chronic use of systemic glucocorticoids. Be aware that patients taking calcium or vitamin D supplements only are not considered to be at risk of MRONJ.

The Scottish Intercollegiate Guidelines Network (SIGN, [www.sign.ac.uk](http://www.sign.ac.uk)) Clinical Guideline 142, *Management of Osteoporosis and the Prevention of Fragility Fractures*,[52](#_ENREF_52) recommends that bisphosphonate therapy should be evaluated every five years to determine if the benefits in continuing therapy outweigh potential risks. As the risk of MRONJ is thought to increase in this patient group as the duration of exposure increases,[12](#_ENREF_12) those patients who continue to take bisphosphonates after this five-year medication review are considered to be at higher risk of MRONJ and their risk level should be reclassified accordingly.

Patients who have taken bisphosphonate drugs at any time in the past and those who have taken denosumab in the last nine months should be assessed and allocated to a risk group as if they are still taking the drugs.

**Risk categories**

The low risk category will include those patients who have been treated for osteoporosis or other non-malignant diseases of bone for less than 5 years and who are not taking concurrent systemic glucocorticoids.

The higher risk category will include cancer patients and also those being treated for osteoporosis or other non-malignant diseases of bone who have other modifying risk factors. The categorisation of these two patient groups in the same higher risk category does not imply that both groups have the same absolute risk level. It simply reflects the need for more considered treatment planning in these higher risk groups.

**MRONJ Risk Assessment**

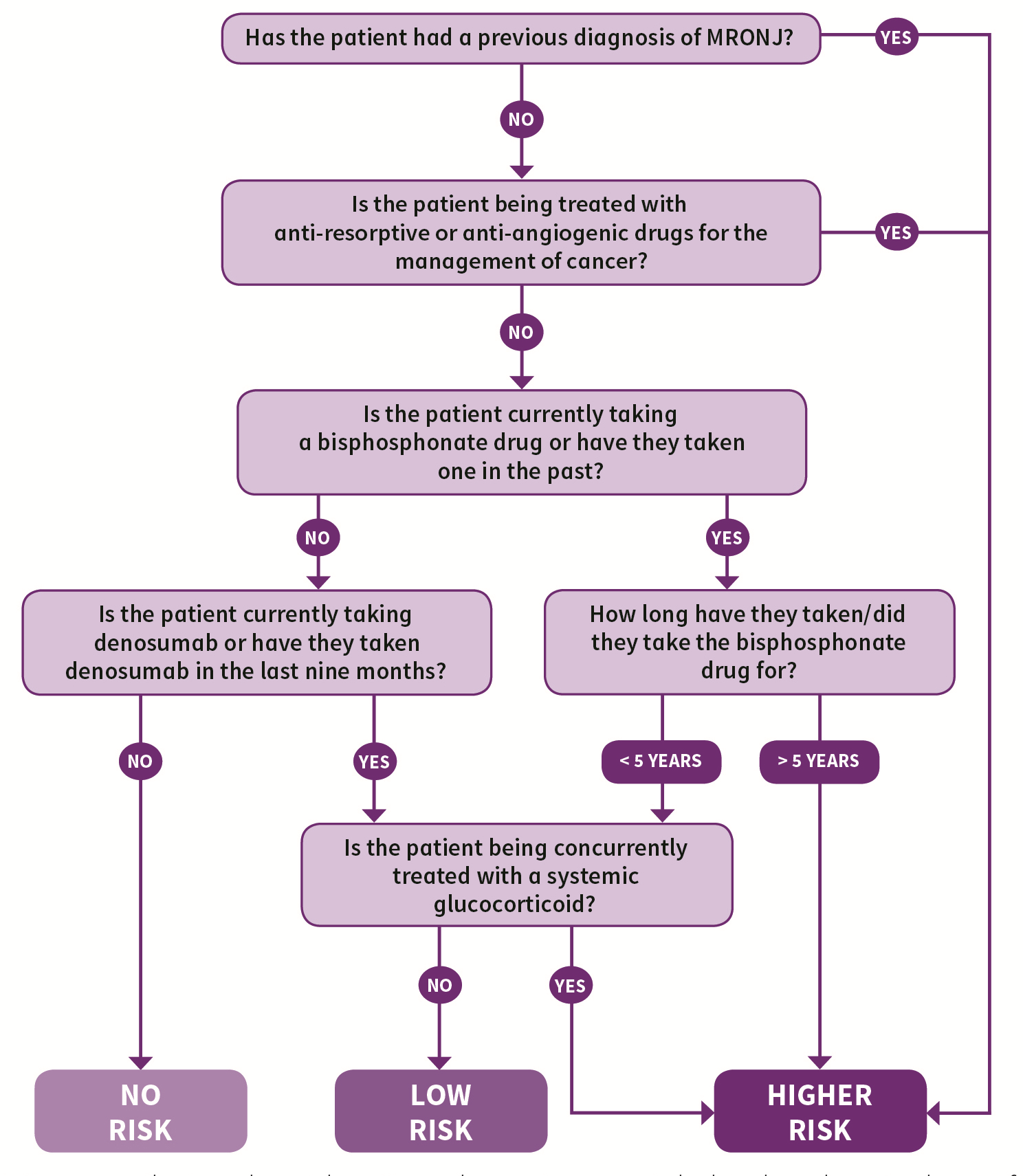
Patients should be allocated to a low or higher risk group based on the characteristics outlined in Table 3.1. The flowchart in Figure 3.1 illustrates how risk should be assessed for each individual patient.

**Table 3.1 Patient Risk Categories**

|  |  |
| --- | --- |
| **Low Risk** if any of the following is present:   * Patients being treated for osteoporosis or other non-malignant diseases of bone (e.g. Paget’s disease) with oral bisphosphonates for **less than 5 years** who are **not** concurrently being treated with systemic glucocorticoids. * Patients being treated for osteoporosis or other non-malignant diseases of bone with quarterly or yearly infusions of intravenous bisphosphonates for **less than 5 years** who are **not** concurrently being treated with systemic glucocorticoids. * Patients being treated for osteoporosis or other non-malignant diseases of bone with denosumab who are **not** being treated with systemic glucocorticoids. | **Higher Risk** if any of the following is present:   * Patients being treated for osteoporosis or other non-malignant diseases of bone (e.g. Paget’s disease) with oral bisphosphonates or quarterly or yearly infusions of intravenous bisphosphonates for **more than 5 years** * Patients being treated for osteoporosis or other non-malignant diseases of bone with bisphosphonates or denosumab **for** **any length of time** who are being concurrently treated with systemic glucocorticoids. * Patients being treated with anti-resorptive or anti-angiogenic drugs (or both) as part of the management of cancer * Patients with a previous diagnosis of MRONJ |

**N.B.** Patients who have taken bisphosphonate drugs at any time in the past and those who have taken denosumab in the last nine months are allocated to a risk group as if they are still taking the drug.

**Figure 3.1 Assessment of Patient Risk**

****

The following best practice advice is based on clinical experience and expert opinion.

* Ask about past, current, or possible future use of anti-resorptive or anti-angiogenic drugs when taking or confirming a medical history.
* The patient (or carer, where appropriate) should have been advised by their prescriber/dispenser about their anti-resorptive or anti-angiogenic drug(s) and the need to inform their dentist.
* Be aware, however, that a patient (or carer) may not know that their medication is an anti-resorptive or anti-angiogenic drug so further in-depth questioning or liaison with their general medical practitioner or medical specialist may be necessary. General questions which may help prompt recall as to whether if patients are taking these drugs include:
  + Have you ever been prescribed a medicine for your bones?
  + Do you take a medicine once a week?
  + Have you ever had a drug infusion for your bones?
  + Do you take long-term steroid tablets for any condition?
* A list of medical conditions that may be managed by anti-resorptive or anti-angiogenic drugs can be found in Appendix 2.
* Assign a level of risk based on an assessment of the medical condition that the patient is being treated for and any other complicating factors such as concurrent glucocorticoid medication and length of exposure to the drugs. See Table 3.1 and Figure 3.1 for further information. Ensure that the assigned risk level is recorded in the patient’s clinical record. Be aware that any low risk patient who continues to take bisphosphonate drugs after their five-year medication review should be reclassified as higher risk.
* If a patient has taken anti-resorptive drugs in the past but is no longer taking them for whatever reason (i.e. completed or discontinued the course or taking a drug holiday), allocate them to a risk group as follows:
* If a patient has taken bisphosphonates in the past, allocate them to a risk group as if they are still taking the drugs.
* If a patient has taken denosumab in the past nine months, allocate them to a risk group as if they are still taking the drug.

N.B. Patients who have previously taken anti-angiogenic drugs in combination with anti-resorptive drugs should be allocated to a risk group based on their history of anti-resorptive drug use.

# 4. Managing Patients at Risk of Medication-related Osteonecrosis of the Jaw (MRONJ)

The overall aim is to manage patients prescribed anti-resorptive or anti-angiogenic drugs in a way that maximises preventive regimes and minimises the need for subsequent extractions and bone trauma, thereby reducing the likelihood of oral complications. However, if extractions or procedures that impact on bone are required, it is likely that these can be performed in the primary care setting. There is no benefit in referring the patient to a specialist or to secondary care based purely on their exposure to anti-resorptive or anti-angiogenic drugs and overall management of these patients is not onerous or difficult. It is also likely to be in patients’ best interests to be treated wherever possible by their own GDP in familiar surroundings.

The following sections detail the oral health management of patients prescribed anti-resorptive or anti-angiogenic drugs. Section 4.1 (Initial Management) encompasses the management of those patients who are about to start, or have very recently started, taking these drugs. Section 4.2 (Continuing Management) covers the management of patients who have an established drug regimen and, for most patients, describes the care required following initial management.

A guide outlining the management of patients prescribed anti-resorptive or anti-angiogenic drugs is presented in Appendix 3.

## 4.1 Initial Management of Patients at Risk of MRONJ

**KEY RECOMMENDATION:**

Before commencement of anti-resorptive or anti-angiogenic drug therapy, or as soon as possible thereafter, aim to get the patient as dentally fit as feasible, prioritising preventive care. Higher risk cancer patients should preferably undergo a thorough dental assessment, with remedial dental treatment where required, prior to commencement of the drug therapy.

(Strong recommendation; low quality evidence)

There is some low quality evidence, mainly based on observational studies, that preventive dental regimes can decrease the risk of oral complications in this patient group by reducing the need for subsequent extractions or other procedures which impact on bone.[53-58](#_ENREF_53) For some patients this may require a change in behaviour in terms of brushing, interdental cleaning and other oral hygiene techniques, as well as other lifestyle behaviours such as diet and tobacco use. There may also be a benefit in prescribing high fluoride toothpaste for those patients with increased caries risk.

For patients who are about to commence treatment with anti-resorptive or anti-angiogenic drugs, or those who have very recently started drug therapy:

* Advise the patient (or carer, where appropriate) that, due to the medication they are taking, there may be a risk of developing MRONJ but ensure that they understand that the risk is small. It is very important that a patient is not discouraged from taking their anti-resorptive or anti-angiogenic medication or from undergoing dental treatment. Record that this advice has been given. A list of points to cover in such a discussion can be found in Appendix 4.
* Give personalised preventive advice to help the patient optimise their oral health, emphasizing the importance of:
* having a healthy diet and reducing sugary snacks and drinks;
* maintaining excellent oral hygiene;
* using fluoride toothpaste and fluoride mouthwash;
* stopping smoking;
* limiting alcohol intake;
* regular dental checks;
* reporting any symptoms such as exposed bone, loose teeth, non-healing sores or lesions, pus or discharge, tingling, numbness or altered sensations, pain or swelling as soon as possible.

Refer to Section 3 of the SDCEP *Prevention and Treatment of Periodontal Diseases in Primary Care*[59](#_ENREF_59) guidance ([www.sdcep.org.uk](http://www.sdcep.org.uk)) for more information on how to discuss these points with patients.

* Prioritise care that will reduce mucosal trauma or may help avoid future extractions or any oral surgery or procedure that may impact on bone:
* consider obtaining appropriate radiographs to identify possible areas of infection and pathology;
* undertake any remedial dental work;
* extract any teeth of poor prognosis without delay;
* focus on minimising periodontal/dental infection or disease;
* adjust or replace poorly fitting dentures to minimise future mucosal trauma;
* consider prescribing high fluoride toothpaste.
* For medically complex patients for whom you would normally seek advice, including higher risk patients who are being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer, consider consulting an oral surgery/special care dentistry specialist with regards to clinical assessment and treatment planning.
* Once the patient is dentally fit, undertake routine dental treatment as outlined in Section 4.2.
* In the situation where a patient presents with an established history of anti-resorptive or anti-angiogenic drug use (e.g. an existing patient who has not attended for some time or a patient new to your practice), follow the advice for extractions or other procedures which impact on bone in low or higher risk patients as outlined in Section 4.2.

N.B. Advise patients who are prescribed an oral bisphosphonate not to hold the tablet in the mouth due to risk of damage to the oral mucosa. Advise patients to follow the instructions for administration given by their doctor or pharmacist or as included in the drug information leaflet.

## 4.2 Continuing Management of Patients at Risk of MRONJ

**KEY RECOMMENDATIONS:**

Carry out all routine dental treatment as normal and continue to provide personalised preventive advice in primary care.

* + Perform straightforward extractions and other bone-impacting treatments in low risk patients in primary care.
  + Adopt a more conservative approach in higher risk patients, giving greater consideration to other, less invasive alternative treatment options before performing extractions and other bone-impacting treatments in primary care.

Do not prescribe antibiotic or antiseptic prophylaxis following extractions or other bone-impacting treatments specifically to reduce the risk of MRONJ.

(Strong recommendations; low quality evidence)

Ongoing management of patients taking anti-resorptive or anti-angiogenic drugs will largely be no different from the routine management of any other patient group. Straightforward extractions and other bone impacting treatments can and should be carried out in primary care and the circumstances for seeking advice from a specialist are the same as for a patient not taking anti-resorptive or anti-angiogenic medication.

Due to the increasing incidence of bacterial resistance and the numerous side effects associated with antibiotic therapy, antibiotics should only be prescribed where there is clear evidence that patients will benefit from them. A review of current literature[60-63](#_ENREF_60) found only observational studies, most of which were underpowered and in some cases had no control group, which generally only included antibiotic and/or antiseptic prophylaxis as one of a combination of measures to prevent MRONJ. There is currently insufficient evidence to support the use of antibiotic or topical antiseptic prophylaxis to reduce the risk of MRONJ following extractions or procedures that impact on bone.

**Low Risk Patients**

See Table 3.1 for a description of patients considered to be at low risk of developing MRONJ.

Having made the patient as dentally fit as feasible:

* Carry out all routine dental treatment as normal and continue to provide personalised preventive advice.
* If an extraction or another procedure that impacts on bone is required:
  + Discuss the risks and benefits associated with treatment with the patient (or carer, where appropriate) to ensure valid consent. See Appendix 4 for points to cover during this discussion;
  + Proceed with the treatment as clinically indicated;
  + Do not prescribe antibiotic or antiseptic prophylaxis unless required for other clinical reasons;
  + Advise the patient to contact the practice if they have any concerns, such as unexpected pain, tingling, numbness, altered sensation or swelling in the extraction area;
  + Review healing. If the extraction socket is not healed at **8 weeks** and you suspect that the patient has MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.
* If you suspect a patient has spontaneous MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.
* Consider reporting any suspected case of MRONJ to the MHRA via the yellow card scheme ([www.yellowcard.mhra.gov.uk](http://www.yellowcard.mhra.gov.uk)) and encourage the patient to do likewise.

N.B. If a MRONJ lesion is confirmed, the oral surgery/special care dentistry specialist will notify you and the patient’s medical practitioner.

**Higher Risk Patients**

See Table 3.1 for a description of patients considered to be at higher risk of developing MRONJ.

Having made the patient as dentally fit as feasible:

* Carry out most routine dental treatment as normal and continue to provide personalised preventive advice.
* For medically complex patients for whom you would normally seek advice, including higher risk patients who are being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer, consider consulting an oral surgery/special care dentistry specialist with regards to clinical assessment and treatment planning.
* If an extraction is indicated, explore all possible alternatives where teeth could potentially be retained e.g. retaining roots in absence of infection.
* If extraction remains the most appropriate treatment:
  + Discuss the risks and benefits associated with treatment with the patient (or carer, where appropriate) to ensure valid consent. See Appendix 4 for points to cover during this discussion;
  + Proceed with the extraction as clinically indicated;
  + Do not prescribe antibiotic or antiseptic prophylaxis unless required for other clinical reasons;
  + Advise the patient to contact the practice if they have any concerns, such as unexpected pain, tingling, numbness, altered sensation or swelling in the extraction area;
  + Review healing. If the extraction socket is not healed at **8 weeks** and you suspect that the patient has MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.
* If you suspect a patient has spontaneous MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.
* Consider reporting any suspected case of MRONJ to the MHRA via the yellow card scheme ([www.yellowcard.mhra.gov.uk](http://www.yellowcard.mhra.gov.uk)) and encourage the patient to do likewise.

N.B. If a MRONJ lesion is confirmed, the oral surgery/special care dentistry specialist will notify you and the patient’s medical practitioner.

# 5. Research and Audit

## 5.1 Recommendations for Research

There is a need for high quality research carried out within an appropriate governance framework to improve the evidence base in the following areas:

* estimation of incidence, particularly for patients with a specific cancer diagnosis;
* risk factors, including oral health status, in patients who develop spontaneous MRONJ;
* incidence of MRONJ following tooth extraction based on the setting (primary or secondary care) where the procedure was performed;
* incidence of MRONJ in patients with implants placed before drug therapy commences and in patients who have implants placed after drug therapy commences;
* efficacy of MRONJ prevention protocols in patients who require an extraction;
* efficacy of proposed treatment strategies for MRONJ.

It may also be beneficial to establish a national database to monitor cases of MRONJ; this could inform some of the research areas highlighted above and may also serve to identify other drugs which could be implicated in the disease.

## 5.2 Recommendations for Audit

Topics for audit and review that could reduce the risk of medication-related osteonecrosis of the jaw include:

* the accuracy and completeness of medical history records;
* assessing patient awareness of MRONJ risk;
* compliance with recommendations within the guidance, for example assigning a MRONJ risk level for each patient taking anti-resorptive or anti-angiogenic drugs.

# Appendix 1 Guidance Development

**The Scottish Dental Clinical Effectiveness Programme**

The Scottish Dental Clinical Effectiveness Programme (SDCEP) is an initiative of the National Dental Advisory Committee (NDAC) and operates within NHS Education for Scotland (NES).

The NDAC comprises representatives of all branches of the dental profession and acts in an advisory capacity to the Chief Dental Officer. It considers issues that are of national importance in Scottish dentistry and also provides feedback to other bodies within the Scottish Government on related, relevant healthcare matters.

SDCEP was established in 2004 under the direction of the NDAC to give a structured approach to providing clinical guidance for the dental profession. The programme’s primary aim is to develop guidance that supports dental teams to provide quality patient care. SDCEP brings together the best available information that is relevant to priority areas in dentistry, and presents guidance on best practice in a form that can be interpreted easily and implemented. The guidance recommendations may be based on a variety of sources of information, including research evidence, guidelines, legislation, policies and expert opinion as appropriate to the subject. SDCEP guidance takes a variety of forms to suit the diverse topics being addressed.

Recognising that publication of guidance alone is likely to have a limited influence on practice, SDCEP also contributes to the research and development of interventions to enhance the translation of guidance recommendations into practice through its participation in the TRiaDS (Translation Research in a Dental Setting) collaboration ([www.triads.org.uk](http://www.triads.org.uk/)).

SDCEP is funded by NHS Education for Scotland and has made important contributions to the implementation of the Scottish Government’s Dental Action Plan, which aims to both modernise dental services and improve oral health in Scotland.

## The Programme Development Team

The Programme Development Team operates within NHS Education for Scotland and is responsible for the methodology of guidance development. Working with members of the Guidance Development Group, the team facilitates all aspects of guidance development by providing project management and administrative support, searching and appraising information and evidence, conducting research, liaising with external organisations, editing the guidance and, managing the publication and dissemination of guidance materials. The following members of the Programme Development Team were directly involved in the development of **Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw.**

|  |  |
| --- | --- |
| Jan Clarkson | Professor of Clinical Effectiveness, University of Dundee; SDCEP Director |
| Doug Stirling | Programme Manager – Guidance and Programme Development |
| Samantha Rutherford | Research and Development Manager – Guidance Development and Lead for this guidance project |
| Linda Young | Research and Development Manager – Evaluation of Implementation |
| Heather Cassie | Research Fellow |
| Laura Lovelock-Hempleman | Clinical Research Dental Hygienist-Therapist |
| Margaret Mooney | Administrator |

For up-to-date information on the full SDCEP Programme Development Team, refer to the SDCEP website ([www.sdcep.org.uk](http://www.sdcep.org.uk)).

## The Guidance Development Group

A Guidance Development Group comprising individuals from a range of relevant branches of the dental profession and other disciplines and two patient representatives was convened to write this guidance.

|  |  |
| --- | --- |
| Michaelina Macluskey  (Co-Chair) | Senior Lecturer/Honorary Consultant Oral Surgeon, Dundee Dental Hospital and School |
| Stephanie Sammut (Co-Chair) | Consultant in Oral Surgery, Dundee Dental Hospital and School |
| Alexander Crighton | Consultant in Oral Medicine, University of Glasgow Dental Hospital and School |
| Helen Devennie | Specialist Practitioner (Medically Compromised and Oral Surgery), Inverness Dental Centre |
| Elizabeth Foster | Patient Representative |
| Karen Gordon | Consultant in Special Care Dentistry, Edinburgh |
| Duncan Gowans | Consultant Haematologist, Ninewells Hospital, Dundee; Perth Royal Infirmary |
| Vicki Greig | Specialty Registrar in Oral Surgery, Greater Glasgow and Clyde |
| Doris Hunter | Patient Representative |
| Douglas Kennedy | Consultant in Oral & Maxillofacial Surgery, NHS Tayside |
| Pamela Kidd | General Dental Practitioner, Glasgow |
| Penny Lockwood | General Medical Practitioner, Dundee; Honorary Senior Clinical Lecturer, University of Dundee |
| Nick Malden | Consultant in Oral Surgery, Edinburgh Dental Institute |
| Anna Macdonald | Senior Dental Officer, Specialist in Special Care Dentistry, Perth |
| Gillian Nevin | General Dental Practitioner, Coupar Angus; Assistant Director of Postgraduate GDP Education, NHS Education for Scotland |
| Terence O’Neill | Professor of Rheumatology and Clinical Epidemiology, University of Manchester; Member of Clinical & Scientific Committee, National Osteoporosis Society |
| David Reid | Emeritus Professor of Rheumatology, University of Aberdeen |
| Andrew Wight | General Dental Practitioner, Dundee |

The Guidance Development Group would like to thank Anne Littlewood, Trials Search Co-ordinator, Cochrane Oral Health Group, for performing the literature searches that underpin the development of this guidance. The Guidance Development Group would also like to acknowledge the contributions of Alison Wright, Gavin Wilson and David Comerford to the evidence appraisal process.

## Guidance Development Methodology

SDCEP endeavours to use a methodology for guidance development that reflects that used to develop high quality guidelines. It aims to be transparent, systematic and to adhere as far as possible to international standards set out by the AGREE (Appraisal of Guidelines for Research and Evaluation) Collaboration ([www.agreetrust.org](http://www.agreetrust.org)). Details of SDCEP guidance development methodology are available at [www.sdcep.org.uk](http://www.sdcep.org.uk).

In 2011, SDCEP published guidance on the **Oral Health Management of Patients Prescribed Bisphosphonates**. This guidance focused exclusively on the risk of osteonecrosis of the jaw in those patients prescribed bisphosphonate drugs, which were the only medications associated with the disease at that time. Since then, several other medications have been implicated in the disease. The guidance has therefore been updated to include these drugs and has been renamed**Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw***.*

Prior to the development of this updated guidance, SDCEP conducted a survey to ascertain dentists’ attitudes towards the first edition of the guidance and to garner feedback on how they felt it could be improved. 197 general dental practitioners responded to the survey and suggestions for improvements were considered during the development of the updated guidance.

For this guidance, a comprehensive search of MEDLINE, EMBASE, CINAHL, AMED, CANCERLIT, Cochrane Database of Systematic Reviews (CDSR), Cochrane Database of Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials (CENTRAL) was conducted by the Trials Search Coordinator of the Cochrane Oral Health Group on the 1st June 2015. Potentially eligible articles were identified independently by two reviewers from the list of titles and abstracts retrieved. An article was considered potentially eligible if it met all of the following criteria:

1. The article was a systematic review or a guideline. An article would be included as a systematic review, if it included a methods section, a search of 1 or more electronic databases and a table of included studies.
2. The article dealt with an aspect of referred to (i) anti-resorptive or anti-angiogenic drugs and (ii) osteonecrosis of the jaw in the context of dental treatment.
3. The article was in English.

Additional manual searching of guideline repositories and other resources, and follow up of citations from relevant articles found through the systematic searching was also carried out.Other sources of evidence identified by GDG members were also considered, taking relevance and methodological quality into account.

A list of clinical questions related to the scope of the guidance was compiled by members of the GDG and eligible articles which were relevant for each question were identified. For the development of this guidance SDCEP used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess and rate the quality of evidence (www.gradeworkinggroup.org). For guidelines, the AGREE II instrument was used, in addition to GRADE, to assess the methodological quality of the retrieved articles (www.agreetrust.org).

The synthesised evidence was summarised and distributed to the GDG to inform and facilitate the development of the recommendations for the guidance. Where authoritative evidence was unavailable, the GDG was asked to make recommendations based on current best practice and expert opinion, reached by consensus. The process for development of recommendations also followed the GRADE approach, with considered judgements based on the quality of evidence, the balance of risks and benefits, the values and preferences of the patients, and the limitations and inconveniences of the treatment.

A twelve-week external consultation was initiated in July 2016. The consultation draft was made available through the SDCEP website and notification of this was sent to a wide range of individuals and organisations with a particular interest in this topic. To obtain feedback from the end-users of the guidance, a small number of dentists were contacted directly to evaluate the guidance, and all dentists in Scotland notified that the consultation draft was available for comment. Targeted external peer review and interviews with general dental practitioners and pharmacists also took place at this time. The literature search was repeated to identify any relevant articles published between June 2015 and August 2016. Following completion of the consultation period and peer review process, all comments were reviewed and considered by the GDG and the guidance amended accordingly prior to publication.

Further information about the methodology used to develop this guidance is available at www.sdcep.org.uk

## Review and Updating

A review of the context of this guidance (evidence, regulations, trends in working practices) will take place three years after publication and, if this has changed significantly, the guidance will be updated accordingly.

## Steering Group

The Steering Group oversees all the activities of the SDCEP and includes representatives of guidance development groups and the dental institutions in Scotland. For up-to-date membership of the Steering Group, refer to the SDCEP website ([www.sdcep.org.uk](http://www.sdcep.org.uk)).

## Conflict of Interest

All contributors to SDCEP are required to declare their financial, intellectual and other relevant interests. At each group meeting, participants are asked to confirm whether there are any changes to these. Should any potential conflicts of interest arise, these are discussed and actions for their management agreed. All declarations of interest and decisions about potential conflicts of interest are available on request.

# Appendix 2 Drugs Associated with MRONJ Prescribed in the United Kingdom\*

**Bisphosphonates**

| **Drug name1** | **Trade name(s)** | **Indication** |
| --- | --- | --- |
| alendronic acid | Binosto®  Fosamax®  Fosavance® | osteoporosis |
| risedronate sodium | Actonel®  Actonel Combi® | osteoporosis  Paget’s Disease |
| zoledronic acid | Aclasta®  Zometa® | osteoporosis  Paget’s Disease  treatment of cancer |
| ibandronic acid | Bondronat®  Bonviva®  Iasibon®  Quodixor® | osteoporosis  treatment of cancer |
| pamidronate disodium | Aredia® | Paget’s Disease  bone pain  treatment of cancer |
| sodium clodronate | Bonefos®  Clasteon®  Loron® | bone pain  treatment of cancer |

1The three most commonly prescribed drugs are listed first

**RANKL Inhibitors**

| **Drug name** | **Trade name(s)** | **Primary Indication** |
| --- | --- | --- |
| denosumab | Prolia®  Xgeva® | osteoporosis  treatment of cancer |

**Anti-angiogenic Drugs**

| **Drug name** | **Trade name(s)** | **Primary Indication** |
| --- | --- | --- |
| bevacizumab | Avastin® | treatment of cancer |
| sunitinib | Sutent® | treatment of cancer |
| aflibercept | Zaltrap® | treatment of cancer |

\*Correct at the time of publication. This list is not exhaustive. Be aware that drug trade names can change and new drugs may be released that may be implicated in MRONJ. Consult the SDCEP website ([www.sdcep.org.uk](http://www.sdcep.org.uk)) for an up-to-date list of the drugs with an MHRA Drug Safety Update for risk of MRONJ.

# Appendix 3 Managing the Oral Health of Patients at Risk of MRONJ

This diagram illustrates the management of patients who are at risk of medication-related osteonecrosis of the jaw (MRONJ). The upper section outlines the initial management of patients who are about to commence treatment with anti-resorptive or anti-angiogenic drugs, or those who have very recently started drug therapy. The lower section outlines the management of patients who require an extraction or procedure which impacts on bone at a later stage in their drug treatment. In the situation where a patient initially presents with an established history of anti-resorptive or anti-angiogenic drug use, follow the advice for extractions or other procedures which impact on bone in the lower section.

# Schematic showing the overall management of pateints at riskog MRONJ.

# Appendix 4 Points to Cover During MRONJ Risk Discussion

**Refer any patient with evi**

**dence of spontaneous MRONJ.**

It is important that patients are not discouraged from taking anti-resorptive or anti-angiogenic drugs or from undergoing dental treatment.

**Points to cover at initial discussion of MRONJ risk**

* Advise the patient that due to medication they are taking, there may be a small risk of developing MRONJ but ensure that they understand that the risk is low.
* Explain that MRONJ is typically diagnosed when there is exposed bone in the jaw that has persisted for 8 weeks and can occur spontaneously or after dental treatment that impacts on bone, such as an extraction. Other symptoms include loose teeth, pain, tingling, numbness, altered sensation or swelling.
* Inform patients with dental implants placed prior to commencement of drug treatment of the small risk of spontaneous MRONJ at those sites.
* Emphasise that MRONJ is an adverse effect of the drug they are taking and is not caused by dental treatment.
* Discuss the benefits of anti-resorptive and/or anti-angiogenic drugs with the patient and why it is important that they continue to take the drugs
* Anti-resorptive drugs significantly reduce the risk of fractures, and subsequent chronic pain, in patients being treated for osteoporosis.
* Anti-angiogenic drugs restrict the growth of tumour blood vessels and are an important part of some cancer treatments. Anti-resorptive drugs reduce bone pain and the risk of fractures in patients being treated for cancer.
* Drug holidays to avoid the risk of MRONJ associated with dental care are not recommended because the benefits of taking the drugs to manage the patient’s medical condition are likely to outweigh the small risk of developing MRONJ and, in the case of the bisphosphonates or denosumab, stopping the drug does not eliminate the risk of developing MRONJ.
* Discuss the overall risk of MRONJ with the patient, based on the medical condition for which they are being treated, using language that they are able to understand. Stress that the risk is small and that the disease is an adverse effect of the medication and is not caused by dental treatment.
* For patients being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer, the risk of MRONJ approximates 1%, (range 0 – 2.3%) which suggests that each patient has a 1 in 100 chance of developing the disease. However, the risk appears to vary based on cancer type and incidence in patients with prostate cancer or multiple myeloma may be higher. Please refer to 2024 supplement for updated incidence information.
* For patients taking anti-resorptive drugs for the prevention or management of non-malignant disease (e.g. osteoporosis, Paget’s disease), the risk of MRONJ approximates 0.1% or less, which suggests that each patient has between a 1 in 1000 and 1 in 10,000 chance of developing the disease.
* Patients who take concurrent glucocorticoid medication or those who are prescribed both anti-resorptive and anti-angiogenic drugs to manage their medical condition may be at higher risk.
* The incidence of MRONJ after tooth extraction is estimated to be 2.9% in patients with cancer and 0.15% in patients being treated for osteoporosis.

The figure below may help you to explain the risk of MRONJ to patients. The frequency is based on the assumption that all included individuals have been exposed to a risk factor, such as a bisphosphonate.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Risk** | 1 in 10 | 1 in 100 | 1 in 1000 | 1 in 10,000 | 1 in 100,000 |
| **Frequency** | Someone in your family | Someone in a street | Someone in a village | Someone in a small town | Someone in a large town |
| **Illustration** |  |  |  |  |  |

Adapted from *Risk Language and Dialects*, Calman and Royston, BMJ 1997; 315:939

* Discuss with the patient the steps that they can take to reduce their risk of MRONJ, including improving their oral hygiene and addressing other lifestyle factors such as diet, smoking status and alcohol consumption.
* More information on techniques to change patient behaviour can be found in Section 3 of the SDCEP Prevention and Treatment of Periodontal Diseases in Primary Care[59](#_ENREF_59) guidance ([www.sdcep.org.uk](http://www.sdcep.org.uk)), including the OH TIPPS behaviour change strategy.
* Encourage patients to attend for regular dental checks and to report any spontaneous symptoms such as exposed bone, loose teeth, non-healing sores or lesions, pus or discharge, tingling, numbness, altered sensation, pain or swelling as soon as possible.

N.B. Advise patients who are prescribed an oral bisphosphonate not to hold the tablet in the mouth due to risk of damage to the oral mucosa. Advise patients to follow the instructions for administration given by their doctor or pharmacist or as included in the drug information leaflet.

* Discuss with the patient the steps you will take to reduce their risk of MRONJ.
* Explain that you will carry out any necessary remedial dental treatment (e.g. extractions, periodontal treatment, refitting appliances or dentures) at an early stage in their medical treatment to ‘future-proof’ their oral health, with the aim of preventing the need for higher risk procedures, such as extractions, in future.
* Patients at higher risk from dental caries may also benefit from high fluoride toothpaste or mouthwash.

**Points to cover when an extraction or procedure that impacts on bone is required**

**Low Risk Patients**

* Inform the patient that although dental treatments that impact on bone, such as extractions, may increase the risk of MRONJ, the risk is still low and the benefits of the dental treatment are likely to outweigh the risks.
* Advise the patient that they will be asked to return after 8 weeks so that you can ensure the extraction socket has healed adequately.
* Patients should also be advised to contact the practice at an earlier date if they have any concerns, such as unexpected pain, numbness, altered sensation or swelling in the extraction area.
* Low risk patients who consider dental implants should be informed of the risk of MRONJ following the procedure and the small risk of long-term implant failure.

**Higher Risk Patients**

* Inform the patient that dental treatments that impact on bone, such as extractions, may increase the risk of MRONJ, therefore all possible alternatives should be considered to avoid extractions where possible. However, there will be cases where extraction is the only treatment option.
* If extraction is the most appropriate option, advise the patient that the benefits of the dental treatment are likely to outweigh the risk of developing MRONJ.
* Advise the patient that they will be asked to return after 8 weeks so that you can ensure the extraction socket has healed adequately.
* Patients should also be advised to contact the practice at an earlier date if they have any concerns, such as unexpected pain, numbness, altered sensation or swelling in the extraction area.

**Patients who have exposed bone at 8 weeks or who present with spontaneous MRONJ**

* Advise the patient that due to the presence of exposed bone in their jaw, they need to be referred to a specialist for further treatment.
* If the patient wishes to know more about the treatment that may be provided in secondary care, advise them that, in general, for cases where only a small amount of bone is exposed treatment may include monitoring, oral hygiene instruction, antibiotics or antibacterial mouth rinses. In cases where a large amount of bone is exposed, surgery may be indicated. However, the treatment they will receive will depend on their individual symptoms and clinical presentation.

# Appendix 5 Guidance for Prescribers and Dispensers of Anti-resorptive or Anti-angiogenic Drugs

You will be aware that anti-resorptive or anti-angiogenic therapy involves a small increased risk of medication-related osteonecrosis of the jaw (MRONJ) and that patients should maintain good oral health to minimise this risk.

Patients who are being prescribed anti-resorptive or anti-angiogenic drugs for the management of cancer should preferably undergo a thorough dental assessment, with remedial dental treatment where required, prior to commencement of the drug therapy.

In addition, the bisphosphonates can cause damage to the oral mucosa therefore it is important that patients (or carers where appropriate) are aware of the need to follow the instructions for administration of these drugs.

* At the commencement of treatment with anti-resorptive or antiangiogenic drugs, advise the patient (or carer where appropriate):
* That the medication they have just been given is associated with a small risk of MRONJ.
* To make an appointment with a dentist as soon as possible to ensure they are dentally fit (this includes patients who have dentures).
* To tell their dentist that they are taking the medication.
* Due to the risk of damage to the oral mucosa, advise patients who are prescribed an oral bisphosphonate not to hold the tablet in the mouth and to follow the instructions for administration included in the drug information leaflet.
* Consider prescribing alternatives to oral bisphosphonates for patients with a poor swallow reflex or swallowing difficulties.

If needed, information about how to find a dentist can be found at www.scottishdental.org, or by phoning the local NHS Health Board.

# Appendix 6 Patient Information

Practices might find it helpful to use a leaflet to provide information to patients prescribed anti-resorptive or anti-angiogenic drugs and as the basis for further discussion. Two patient information leaflets, one for those being treated for osteoporosis or other non-malignant diseases of bone and one for patients with cancer, are available to download from [www.sdcep.org.uk](http://www.sdcep.org.uk).

# References

1. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw - 2014 update. Journal of Oral and Maxillofacial Surgery. 2014;72(10):1938-1956.

2. Khan AA, Morrison A, Hanley DA, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. Journal of Bone and Mineral Research. 2015;30(1):3-23.

3. Qi WX, Tang LN, He AN, Yao Y, Shen Z. Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: a meta-analysis of seven randomized controlled trials. International Journal of Clinical Oncology. 2014;19(2):403-410.

4. Lee SH, Chang SS, Lee M, Chan RC, Lee CC. Risk of osteonecrosis in patients taking bisphosphonates for prevention of osteoporosis: a systematic review and meta-analysis. Osteoporosis International. 2014;25(3):1131-1139.

5. Kuhl S, Walter C, Acham S, Pfeffer R, Lambrecht JT. Bisphosphonate-related osteonecrosis of the jaws - a review. Oral Oncology. 2012;48(10):938-947.

6. Guarneri V, Miles D, Robert N, et al. Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. Breast Cancer Research and Treatment. 2010;122(1):181-188.

7. Carmona EG, Flores AG, Santamaría EL, Olea AH, Lozano MPR. Systematic literature review of biphosphonates and osteonecrosis of the jaw in patients with osteoporosis. Reumatologia Clinica. 2013;9(3):172-177.

8. Solomon DH, Mercer E, Woo SB, Avorn J, Schneeweiss S, Treister N. Defining the epidemiology of bisphosphonate-associated osteonecrosis of the jaw: prior work and current challenges. Osteoporosis International. 2013;24(1):237-244.

9. Hellstein JW, Adler RA, Edwards B, et al. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: executive summary of recommendations from the American Dental Association Council on Scientific Affairs. Journal of the American Dental Association. 2011;142(11):1243-1251.

10. Rogers SN, Palmer NO, Lowe D, Randall C. United Kingdom nationwide study of avascular necrosis of the jaws including bisphosphonate-related necrosis. The British Journal of Oral & Maxillofacial Surgery. 2015;53(2):176-182.

11. Sammut S, Malden N, Lopes V, Ralston S. Epidemiological study of alendronate-related osteonecrosis of the jaw in the southeast of Scotland. The British Journal of Oral & Maxillofacial Surgery. 2016;54(5):501-505.

12. Lo JC, O'Ryan FS, Gordon NP, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. Journal of Oral and Maxillofacial Surgery. 2010;68(2):243-253.

13. Grbic JT, Black DM, Lyles KW, et al. The incidence of osteonecrosis of the jaw in patients receiving 5 milligrams of zoledronic acid: data from the health outcomes and reduced incidence with zoledronic acid once yearly clinical trials program. Journal of the American Dental Association. 2010;141(11):1365-1370.

14. Prolia 60 mg solution in a pre-filled syringe: Summary of Product Characteristics. Amgen Ltd. 2016; ([www.medicines.org.uk/emc/medicine/23127](http://www.medicines.org.uk/emc/medicine/23127). Accessed 01/12/16).

15. Khan SA, Kanis JA, Vasikaran S, et al. Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. Journal of Bone and Mineral Research. 1997;12(10):1700-1707.

16. Landesberg R, Cozin M, Cremers S, et al. Inhibition of Oral Mucosal Cell Wound Healing by Bisphosphonates. Journal of Oral and Maxillofacial Surgery. 2008;66(5):839-847.

17. Reid IR, Bolland MJ, Grey AB. Is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? Bone. 2007;41(3):318-320.

18. Landesberg R, Woo V, Cremers S, et al. Potential pathophysiological mechanisms in osteonecrosis of the jaw. Annals of the New York Academy of Sciences. 2011;1218:62-79.

19. Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. The Journal of Clinical Endocrinology and Metabolism. 2011;96(4):972-980.

20. MHRA. Bevacizumab and sunitinib: risk of osteonecrosis of the jaw. Drug Safety Update. Jan 2011;4(6):A1.

21. MHRA. Aflibercept (Zaltrap): minimising the risk of osteonecrosis of the jaw. Drug Safety Update. Apr 2016;9(9).

22. Rollason V, Laverriere A, MacDonald LC, Walsh T, Tramer MR, Vogt-Ferrier NB. Interventions for treating bisphosphonate-related osteonecrosis of the jaw (BRONJ). The Cochrane Database of Systematic Reviews. 2016;2:CD008455.

23. Ngan KK, Bowe J, Goodger N. The risk of bisphosphonate-related osteonecrosis of the jaw in children. A case report and literature review. Dental Update. 2013;40(9):733-734, 736-738.

24. Bhatt RN, Hibbert SA, Munns CF. The use of bisphosphonates in children: review of the literature and guidelines for dental management. Australian Dental Journal 2014;59(1):9-19.

25. Hennedige AA, Jayasinghe J, Khajeh J, Macfarlane TV. Systematic review on the incidence of bisphosphonate related osteonecrosis of the jaw in children diagnosed with osteogenesis imperfecta. Journal of Oral & Maxillofacial Research. 2013;4(4):e1.

26. Thumbigere-Math V, Michalowicz BS, Hodges JS, et al. Periodontal disease as a risk factor for bisphosphonate-related osteonecrosis of the jaw. Journal of Periodontology. 2014;85(2):226-233.

27. Schipmann S, Metzler P, Rossle M, et al. Osteopathology associated with bone resorption inhibitors - which role does Actinomyces play? A presentation of 51 cases with systematic review of the literature. Journal of Oral Pathology & Medicine. 2013;42(8):587-593.

28. Gaudin E, Seidel L, Bacevic M, Rompen E, Lambert F. Occurrence and risk indicators of medication-related osteonecrosis of the jaw after dental extraction: a systematic review and meta-analysis. Journal of Clinical Periodontology. 2015;42(10):922-932.

29. Fehm T, Beck V, Banys M, et al. Bisphosphonate-induced osteonecrosis of the jaw (ONJ): Incidence and risk factors in patients with breast cancer and gynecological malignancies. Gynecologic Oncology. 2009;112(3):605-609.

30. Saad F, Brown JE, Van Poznak C, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Annals of Oncology. 2012;23(5):1341-1347.

31. Vahtsevanos K, Kyrgidis A, Verrou E, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. Journal of Clinical Oncology. 2009;27(32):5356-5362.

32. Yazdi PM, Schiodt M. Dentoalveolar trauma and minor trauma as precipitating factors for medication-related osteonecrosis of the jaw (ONJ): a retrospective study of 149 consecutive patients from the Copenhagen ONJ Cohort. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2015;119(4):416-422.

33. Nisi M, La Ferla F, Karapetsa D, et al. Risk factors influencing BRONJ staging in patients receiving intravenous bisphosphonates: a multivariate analysis. International Journal of Oral and Maxillofacial Surgery. 2015;44(5):586-591.

34. Otto S, Troltzsch M, Jambrovic V, et al. Tooth extraction in patients receiving oral or intravenous bisphosphonate administration: A trigger for BRONJ development? Journal of Cranio-maxillo-facial Surgery. 2015;43(6):847-854.

35. Taylor T, Bryant C, Popat S. A study of 225 patients on bisphosphonates presenting to the bisphosphonate clinic at King's College Hospital. British Dental Journal. 2013;214(7):E18.

36. Tsao C, Darby I, Ebeling PR, et al. Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. Journal of Oral and Maxillofacial Surgery. 2013;71(8):1360-1366.

37. Kos M, Brusco D, Kuebler J, Engelke W. Clinical comparison of patients with osteonecrosis of the jaws, with and without a history of bisphosphonates administration. International Journal of Oral and Maxillofacial Surgery. 2010;39(11):1097-1102.

38. Lazarovici TS, Yahalom R, Taicher S, Elad S, Hardan I, Yarom N. Bisphosphonate-related osteonecrosis of the jaws: a single-center study of 101 patients. Journal of Oral and Maxillofacial Surgery. 2009;67(4):850-855.

39. Lazarovici TS, Yahalom R, Taicher S, Schwartz-Arad D, Peleg O, Yarom N. Bisphosphonate-related osteonecrosis of the jaw associated with dental implants. Journal of Oral and Maxillofacial Surgery. 2010;68(4):790-796.

40. Ata-Ali J, Ata-Ali F, Penarrocha-Oltra D, Galindo-Moreno P. What is the impact of bisphosphonate therapy upon dental implant survival? A systematic review and meta-analysis. Clinical Oral Implants Research. 2016;27(2):e38-46.

41. Chadha GK, Ahmadieh A, Kumar S, Sedghizadeh PP. Osseointegration of dental implants and osteonecrosis of the jaw in patients treated with bisphosphonate therapy: a systematic review. Journal of Oral Implantology. 2013;39(4):510-520.

42. Famili P, Quigley S, Mosher T. Survival of dental implants among post-menopausal female dental school patients taking oral bisphosphonates: a retrospective study. Compendium of Continuing Education in Dentistry. 2011;32(6):E106-109.

43. Koka S, Babu NM, Norell A. Survival of dental implants in post-menopausal bisphosphonate users. Journal of Prosthodontic Research. 2010;54(3):108-111.

44. Liddelow G, Klineberg I. Patient-related risk factors for implant therapy. A critique of pertinent literature. Australian Dental Journal. 2011;56(4):417-426; quiz 441.

45. Mozzati M, Arata V, Giacomello M, et al. Failure risk estimates after dental implants placement associated with plasma rich in growth factor-endoret in osteoporotic women under bisphosphonate therapy. Journal of Craniofacial Surgery. 2015;26(3):749-755.

46. Giovannacci I, Meleti M, Manfredi M, et al. Medication-Related Osteonecrosis of the Jaw Around Dental Implants: Implant Surgery-Triggered or Implant Presence-Triggered Osteonecrosis? Journal of Craniofacial Surgery. 2016;27(3):697-701.

47. Goss A, Bartold M, Sambrook P, Hawker P. The nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in dental implant patients: a South Australian case series. Journal of Oral and Maxillofacial Surgery. 2010;68(2):337-343.

48. Holzinger D, Seemann R, Matoni N, Ewers R, Millesi W, Wutzl A. Effect of dental implants on bisphosphonate-related osteonecrosis of the jaws. Journal of Oral and Maxillofacial Surgery. 2014;72(10):1937.e1931-1938.

49. Kwon TG, Lee CO, Park JW, Choi SY, Rijal G, Shin HI. Osteonecrosis associated with dental implants in patients undergoing bisphosphonate treatment. Clinical Oral Implants Research. 2014;25(5):632-640.

50. Matsuo A, Hamada H, Takahashi H, Okamoto A, Kaise H, Chikazu D. Evaluation of dental implants as a risk factor for the development of bisphosphonate-related osteonecrosis of the jaw in breast cancer patients. Odontology. 2015; 104: 363-371.

51. Montoya-Carralero JM, Parra-Mino P, Ramirez-Fernandez P, Morata-Murcia IM, Mompean-Gambin Mdel C, Calvo-Guirado JL. Dental implants in patients treated with oral bisphosphonates: a bibliographic review. Medicina Oral, Patologia Oral y Cirugia Bucal. 2010;15(1):e65-69.

52. Management of Osteoporosis and the Prevention of Fragility Fractures. (SIGN Publication No. 142). Scottish Intercollegiate Guidelines Network; 2015.

53. Kyrgidis A, Tzellos TG, Toulis K, Arora A, Kouvelas D, Triaridis S. An evidence-based review of risk-reductive strategies for osteonecrosis of the jaws among cancer patients. Current Clinical Pharmacology. 2013;8(2):124-134.

54. Bramati A, Girelli S, Farina G, et al. Prospective, mono-institutional study of the impact of a systematic prevention program on incidence and outcome of osteonecrosis of the jaw in patients treated with bisphosphonates for bone metastases. Journal of Bone and Mineral Metabolism. 2015;33(1):119-124.

55. Vandone AM, Donadio M, Mozzati M, et al. Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: a single-center clinical experience. Annals of Oncology. 2012;23(1):193-200.

56. Bonacina R, Mariani U, Villa F, Villa A. Preventive strategies and clinical implications for bisphosphonate-related osteonecrosis of the jaw: a review of 282 patients. Journal of the Canadian Dental Association. 2011;77:b147.

57. Francini F, Pascucci A, Francini E, et al. Osteonecrosis of the jaw in patients with cancer who received zoledronic acid and bevacizumab. Journal of the American Dental Association. 2011;142(5):506-513.

58. Ripamonti CI, Maniezzo M, Campa T, et al. Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan. Annals of Oncology. 2009;20(1):137-145.

59. Prevention and Treatment of Periodontal Diseases in Primary Care. Scottish Dental Clinical Effectiveness Programme; 2014.

60. Ferlito S, Puzzo S, Liardo C. Preventive protocol for tooth extractions in patients treated with zoledronate: a case series. Journal of Oral and Maxillofacial Surgery. 2011;69(6):e1-4.

61. Lodi G, Sardella A, Salis A, Demarosi F, Tarozzi M, Carrassi A. Tooth extraction in patients taking intravenous bisphosphonates: a preventive protocol and case series. Journal of Oral and Maxillofacial Surgery. 2010;68(1):107-110.

62. Mozzati M, Arata V, Gallesio G. Tooth extraction in osteoporotic patients taking oral bisphosphonates. Osteoporosis International. 2013;24(5):1707-1712.

63. Schubert M, Klatte I, Linek W, et al. The saxon bisphosphonate register - therapy and prevention of bisphosphonate-related osteonecrosis of the jaws. Oral Oncology. 2012;48(4):349-354.

1. ǂEstimate based on data extracted from primary studies by Khan et al.2 [↑](#footnote-ref-2)