Scottish Dental
Clinical Effectiveness Programme

Oral Health Management of Patients Prescribed Anti-resorptive or Anti-angiogenic Drugs

Dental Clinical Guidance

Draft - For Consultation Only

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As this is a consultation draft, any changes to practice should only be considered after the final version is published.

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Summary Guidance

Risk Assessment

- Allocate the patient to a risk group (as below) and record this in the clinical notes.‡

Low Risk	Higher Risk
Patients being treated for osteoporosis or other non-malignant diseases of bone with: • oral (or yearly infusions of i.v.) bisphosphonates for **less than 5 years**, *or* • RANKL inhibitors (e.g. denosumab) who are **not** taking concurrent systemic corticosteroid or other immuno-suppressant medication.	Patients who have been treated for osteoporosis or other non-malignant diseases of bone with: • oral (or yearly infusions of i.v.) bisphosphonates for **more than 5 years**, *or* • oral (or yearly infusions of i.v.) bisphosphonates or RANKL inhibitors (e.g. denosumab) **for any length of time** with concurrent use of systemic corticosteroids or other immuno-suppressants; Patients taking an anti-resorptive or anti-angiogenic drug (or both) as part of the management of cancer; Patients with a previous diagnosis of MRONJ.

‡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 RANKL inhibitors (e.g. denosumab) in the past six months, allocate them to a risk group as if they are still taking the drugs.

Initial Management

- Advise the patient that there is a risk of developing medication-related osteonecrosis of the jaw (MRONJ) but ensure they understand it is a rare condition so that they are not discouraged from taking their medication or undergoing dental treatment. Record that this advice has been given.
- As soon as possible, aim to get the patient as dentally fit as feasible by prioritising remedial work, reducing sources of dental infection and adjusting poorly fitting dentures. Extract teeth of poor prognosis without delay.* Consider prescribing high fluoride toothpaste.

*If a patient first 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 the Continuing Management section below.

- For higher risk, medically complex patients who are being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer and for whom you would normally seek advice, consider consulting an oral surgery/special care dentistry specialist with regards to treatment planning and continuing management.
- Maximise preventive regimes to minimise risk of future extractions and bone trauma.
- Give preventive advice, emphasizing the importance of a healthy diet, maintaining good oral hygiene, using fluoride toothpaste, stopping smoking, limiting alcohol intake, and regular dental checks. Encourage patients to report any symptoms such as loose teeth, numbness, pain, or swelling as soon as possible.

Continuing Management

- Treat routinely for scale and polish, simple restorations, recall and radiological review.
- If any extraction or any oral surgery or procedure which may impact on bone is necessary, discuss the risk of the procedure with the patient to ensure informed consent and follow the recommended management strategy for each patient based on their allocated risk group.

Low Risk	Higher Risk
• Perform extractions and procedures that may impact on bone in primary care. • Do not prescribe antibiotic or antiseptic prophylaxis;	• Explore all possible alternatives to extraction where teeth could potentially be retained e.g. retaining roots in absence of infection. • If extraction remains the most appropriate treatment, proceed as for low risk patients.

- Review healing at 8 weeks and if there is evidence of MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.
- **If a patient has evidence of spontaneous MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.**

Oral Health Management of Patients Prescribed Anti-resorptive or Anti-angiogenic Drugs

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, 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 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. The impact of potential barriers identified during guidance development and through stakeholder involvement and external consultation was also considered when formulating the recommendations.

This process for 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. 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 dental 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. These advice points are indicated with molar bullet points (●).

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.

2. Medication-related Osteonecrosis of the Jaw

2.1 What is Medication-related Osteonecrosis of the Jaw (MRONJ)?

MRONJ 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]

Although most 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] 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 other drugs such as systemic corticosteroids and other immunosuppressants, dentoalveolar surgery and mucosal trauma.

Incidence in Cancer Patients

Estimates of incidence and prevalence vary due to the rare nature of the disease. In cancer patients being treated with intravenous anti-resorptive drugs, the risk for MRONJ ranges from 0 to 12% (0-1200 cases per 10,000)[2-5] 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] 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%).‡ This agrees with an estimate of MRONJ risk based on studies with Level 1 evidence (systematic reviews or RCTs).[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] 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]

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),[1,2,5,7-9] with a recent UK study estimating incidence to be 'more than 1 in 10,000 and less than 1 in 1000'.[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] There is some weak evidence that the risk appears to increase with increasing drug duration.[12] The risk of MRONJ in patients with osteoporosis given a once yearly intravenous infusion of bisphosphonates

‡Estimate based on data extracted from primary studies by Khan et al.[2]

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] There is less evidence to base an estimate of incidence in those patients prescribed RANKL inhibitors (e.g. denosumab). One report of an ongoing phase III clinical study found a risk of MRONJ of 0.04% (4 cases per 10,000) in this patient group.[14]

These figures illustrate that MRONJ is a rare condition, and although the risk should be discussed with patients, it is very 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 the receptor activator of nuclear factor κB ligand (RANKL) inhibitors (e.g. 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] 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.[16,17] There is also some evidence that these drugs can inhibit angiogenesis.[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 corticosteroids 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.

RANKL Inhibitors

Denosumab is an example of a RANKL inhibitor. It is a humanised 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 and monthly in patients with metastatic disease. Denosumab does not bind to bone and its effects on bone turnover diminish within six months of treatment completion.[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.

The vascular 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 MHRA has issued Drug Safety Updates identifying MRONJ as a possible side effect of these drugs.[20,21]

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] 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] 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.

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.

The length of time that the patient has been exposed to the drug(s) and the concurrent use of other medication, such as chemotherapy or systemic corticosteroids, are also considered risk factors. Patients who have had a previous episode of MRONJ are also considered as being at higher risk.

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.[23,24] However, MRONJ can occur 'spontaneously' without the patient having undergone any recent invasive dental treatment.

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 until the month prior to the patient's next scheduled drug administration.

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 RANKL inhibitors (e.g. denosumab) on bone turnover diminishes within six months of treatment completion. Therefore, after this time, the risk of MRONJ will be the same as a patient who has never taken the drugs.

Anti-angiogenic drugs are not thought to remain in the body for extended periods of time. Therefore, the risk of MRONJ for patients who have discontinued these drugs is likely to be the same as a patient who has never taken the drugs.

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 therapy and any other complicating factors and record this in the patient's clinical notes.
(Strong recommendation; low quality evidence)

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 or anti-angiogenic drugs and to identify any additional risk factors, such as chronic use of systemic corticosteroids. 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. Patients should be allocated to a low or higher risk group based on the characteristics outlined in Table 3.1. Patients who have taken bisphosphonate drugs at any time in the past and those who have taken RANKL inhibitors (e.g. denosumab) in the last six months should be allocated to a risk group as if they are still taking the drugs.

Table 3.1 Assessment of Patient Risk

Low Risk if any of the following is present:	**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 for **less than 5 years** who are **not** concurrently being treated with systemic corticosteroids or other immuno-suppressants	• Patients being treated for osteoporosis or other non-malignant diseases of bone (e.g. Paget's disease) with oral bisphosphonates or yearly infusions of intravenous bisphosphonates for **more than 5 years**
• Patients being treated for osteoporosis or other non-malignant diseases of bone with yearly infusions of intravenous bisphosphonates for **less than 5 years** who are **not** concurrently being treated with systemic corticosteroids or other immuno-suppressants	• Patients being treated for osteoporosis or other non-malignant diseases of bone with bisphosphonates or RANKL inhibitors (e.g. denosumab) **for any length of time** who are being concurrently treated with systemic corticosteroids or other immuno-suppressants
• Patients being treated for osteoporosis or other non-malignant diseases of bone with RANKL inhibitors (e.g. denosumab) who are **not** being treated with systemic corticosteroids or other immuno-suppressants	• Patients taking an anti-resorptive or anti-angiogenic drug (or both) as part of the management of cancer • Patients with a previous diagnosis of MRONJ

N.B. Patients being treated for osteoporosis with calcium or vitamin D supplements only are at no risk of MRONJ.

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 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 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 determine if patients are taking these drugs include:
        - Have you ever been prescribed a medicine for your bones?
        - Have you ever had a drug infusion for your bones?
        - Are you taking prolonged systemic steroids/oral steroids, such as prednisolone, 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 medication (corticosteroids or other immunosuppressants) and length of exposure to the drugs. See Table 3.1 for further information. Ensure that the assigned risk level is recorded in the patient's clinical record.
- If a patient has taken these 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 RANKL inhibitors (e.g. denosumab) in the past six months, allocate them to a risk group as if they are still taking the drugs. If it has been more than six months since they discontinued their drug treatment, they are no longer considered to be at risk of MRONJ*.
    - Patients who have taken antiangiogenic drugs in the past are no longer considered to be at risk of MRONJ once they discontinue drug treatment*.

*Patients who have taken these drugs in combination with a bisphosphonate should be allocated to a risk group based on their history of bisphosphonate use.

4. Managing Patients Prescribed Anti-resorptive or Anti-angiogenic Drugs

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.

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 Prescribed Anti-resorptive or Anti-angiogenic Drugs

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 preventative care.
(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.[25-30] 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.

- Advise the patient that, due to the medication they are taking, there may be a risk of developing MRONJ but ensure that they understand that it is a rare condition. 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 or fluoride mouthwash;
  - stopping smoking;
  - limiting alcohol intake;
  - regular dental checks;
  - reporting any symptoms such as loose teeth, numbness or altered sensations, pain or swelling as soon as possible.
- 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 an OPT radiograph
  - undertake any remedial dental work;

- extract any teeth of poor prognosis without delay*;
- focus on reducing periodontal/dental infection or disease;
- adjust or replace poorly fitting dentures to minimise future mucosal trauma;
- consider prescribing high fluoride toothpaste.

- For higher risk, medically complex patients who are being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer and for whom you would normally seek advice, 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 included in the drug information leaflet.

4.2 Continuing Management of Patients Prescribed Anti-resorptive or Anti-angiogenic Drugs

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

(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.

Antibiotic Prophylaxis

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[31-34] 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 to ensure informed 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;
        - Review healing at **8 weeks** and if there is evidence of MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.
- If a patient has evidence of spontaneous MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.

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 higher risk, medically complex patients who are being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer and for whom you would normally seek advice, consider consulting an oral surgery/special care dentistry specialist with regards to treatment planning and continuing management.
- 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 and consent patient for procedure (see Appendix 5);
        - Proceed with the extraction as clinically indicated;
        - Do not prescribe antibiotic or antiseptic prophylaxis;
        - Review healing as at 8 weeks, and if there is evidence of MRONJ refer to an oral surgery/special care dentistry specialist as per local protocols
- If a patient has evidence of spontaneous MRONJ, refer to an oral surgery/special care dentistry specialist as per local protocols.

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).

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. For up-to-date information on the SDCEP Programme Development Team, refer to the SDCEP website (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.

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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). Details of SDCEP guidance development methodology are available at 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 Prescribed Anti-resorptive or Anti-angiogenic Drugs*.

Prior to the development of this updated guidance, SDCEP conducted a survey to ascertain dentists' attitudes towards 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. All comments received through the consultation process will be considered by the GDG and the guidance amended accordingly prior to publication.

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).

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 name[1]	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

[1]The three most commonly prescribed drugs are listed first

RANKL Inhibitors

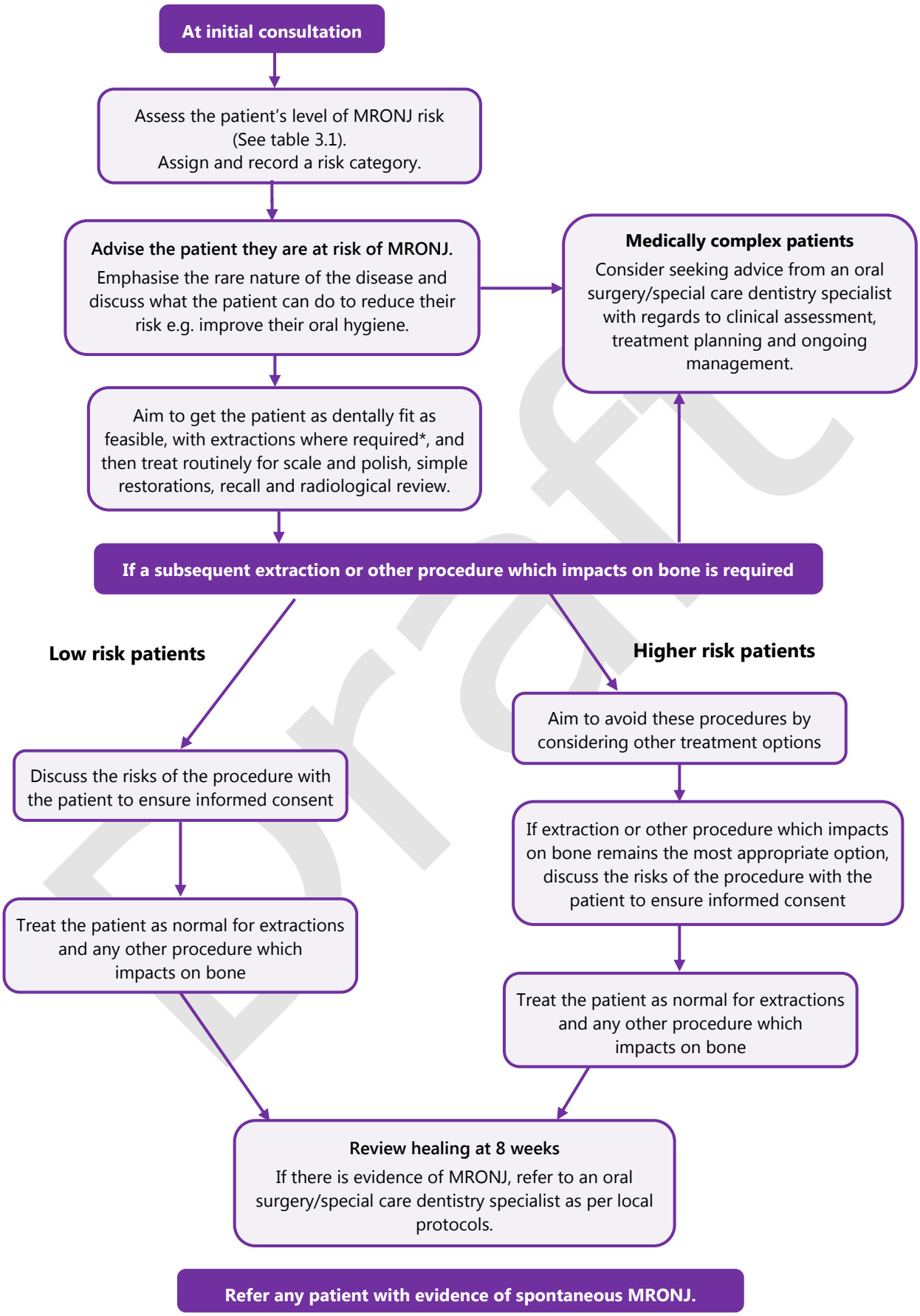
Drug name	Trade name(s)	Primary Indication
denosumab	Prolia® Xgeva®	osteoporosis treatment of cancer

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.

Appendix 3 Managing a Dental Patient Taking Anti-resorptive or Anti-angiogenic Drugs



*In the situation where a patient 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 low or higher risk patients as outlined in the second half of the flow diagram.

Appendix 4 Points to Cover During MRONJ Risk Discussion

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 it is a rare condition.
- 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 reduce the risk of fractures 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 outweigh the small risk of developing MRONJ and, in the case of the bisphosphonates or RANKL inhibitors, 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 disease is rare, 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.
  - For patients taking oral 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 medication, such as systemic corticosteroids or other immunosuppressants, or those who are prescribed both anti-resorptive and anti-angiogenic drugs to manage their medical condition may be at higher risk.
- 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.
  - Encouraging patients to change their behaviour can be challenging. Advice which is individualised to each patient has been shown to be effective,[35] as has the use of action plans.[36] 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*[37] guidance (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 loose teeth, pain, numbness, altered sensation or swelling as soon as possible.
- Discuss with the patient the steps you will take to reduce their risk of MRONJ.
  - Explain that you are carrying 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.

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 remains the most appropriate option, advise the patient that the benefits of the dental treatment are likely to outweigh the risks 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 very small increased risk of impaired wound healing in the mouth and that the patient should maintain good oral health to minimise the risk of medication-related osteonecrosis of the jaw (MRONJ).

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.

- Advise the patient (or carer where appropriate):
  - That the medication they have just been given is associated with a very 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 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 this leaflet to provide information to patients prescribed anti-resorptive or anti-angiogenic drugs and as the basis for further discussion. This leaflet can be downloaded from www.sdcep.org.uk.

Dental advice for patients prescribed anti-resorptive or anti-angiogenic drugs

Why have I been given this leaflet?

You have told your dentist that you are taking a drug that might affect the way some bones work. There is a very small risk for developing a condition called medication-related osteonecrosis of the jaw (MRONJ).

What is the risk for developing MRONJ?

The risk of developing MRONJ is very low as this is an extremely rare condition. However, some other medical problems that you may have might slightly increase your risk.

Should I stop taking the drug?

No, continue to take your medication. The medical benefits far outweigh the risks. Talk with your doctor and dentist if you have any questions.

What are the risks associated with dental treatment?

The risk is very low to non-existent for most ordinary treatments. The risk is increased if you require treatment that affects bone (like a tooth extraction) but is still considered low.

What are the risks associated with not having dental treatment?

You may be at increased risk of developing other health problems if a dental disease is not treated. Your dentist will be able to discuss alternative treatment options and the risks associated with them. You should also consult with your doctor about any health risks.

Can I decrease my risk of developing MRONJ?

There are several things you can do to reduce the risk:

Visit your dentist for regular dental check-ups
Your dentist will monitor your oral health to ensure that any dental disease that may develop is treated before dental surgery is required.

Ensure that you tell your dentist about all the medications you are taking and your medical history
Tell your dentist about any health problems that you have and all medicines that you are taking so that the dentist can assess your individual risk for developing MRONJ.

Talk to your dentist about oral hygiene
Maintaining good oral hygiene is the best way to prevent oral diseases that may require dental surgery.

What else can I do?

Stop smoking
Smoking can affect your oral health. Call Smokeline (0800 84 84 84) or go to www.canstopsmoking.com.

Reduce the frequency of sugary snacks and drinks
Regular consumption of sugary snacks and drinks can lead to tooth decay.

Reduce the amount of alcohol you drink
Regular heavy alcohol consumption can increase your risk of developing some dental diseases.

Are there signs and symptoms I should look out for?

You should contact your dentist immediately if you notice any of the following symptoms:

- Feeling of numbness, heaviness or other unusual sensations in your jaw
- Pain in your jaw or a bad taste
- Swelling of your jaw
- Loose teeth
- Exposed bone

Remember, MRONJ is very rare and the benefits of taking the drug you have been prescribed far outweigh the risks. Looking after your oral health will reduce your risk even more.

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