7.1 **GENERAL PRINCIPLES**

- Bisphosphonates are synthetic analogues of pyrophosphate, a natural regulator of bone metabolism found abundantly in bone matrix. They inhibit differentiation of osteoclast precursors and induce osteoclast apoptosis leading to a decrease in bone resorption.\(^1\), \(^2\)

- Bisphosphonates may be classified into two main groups:
  - The more potent nitrogen-containing bisphosphonates inhibit osteoclast bone resorption by inhibition of the mevalonate pathway. They include zoledronic acid, disodium pamidronate and ibandronic acid.
  - The less potent non-nitrogen containing bisphosphonates form cytotoxic ATP analogues interfering with cellular metabolism. They include disodium clodronate and disodium etidronate.\(^1\), \(^2\)

- Zoledronic acid, disodium pamidronate and ibandronic acid are the most potent and widely used bisphosphonates for the management of metastatic bone disease.\(^3\)

- Ibandronic acid is available in oral and intravenous preparations. It is only licensed for the management of metastatic bone disease in patients with metastatic breast cancer.\(^4\), \(^5\)
  
  Local policies may dictate which bisphosphonate is available for clinical use.

- Bisphosphonates, and in particular the aminobisphosphonates, are known to have a number of side effects. These include a rise in body temperature and accompanying flu-like symptoms that resemble a typical acute phase response. Other side effects include renal toxicity, hypocalcaemia and osteonecrosis of the jaw.\(^6\)

7.2 **GUIDELINES**

7.2.1 **Initiation, dosing and duration of treatment**

- Treatment with opioids and NSAIDs should be optimised before using bisphosphonates for pain relief. Consider referral for radiotherapy or orthopaedic interventions where appropriate.\(^7\) [Level 4]

- Bisphosphonates should be considered where clinically appropriate for the prevention of skeletal related events and treatment of malignant bone pain in patients with bone metastases from breast cancer or hormone refractory prostate cancer and in patients with multiple myeloma.\(^1\), \(^7\)-\(^9\), \(^10\) [Level 1+] Decisions to treat should be based on an assessment of their general medical condition and expected survival time.\(^11\) [Level 4]

- In patients with lung, renal or solid tumours (other than breast or prostate) metastasizing to bone, the strongest evidence is for the use of zoledronic acid to delay the onset of skeletal related events.\(^1\) [Level 2]

- Zoledronic acid should be the current bisphosphonate of choice for patients with hormone refractory prostate cancer with bone metastases. This is for both prevention of skeletal related events and palliation of bone pain.\(^6\) [Level 2++]
- If using zoledronic acid, the datasheet recommends the use of oral calcium supplements 500mg daily plus vitamin D 400 IU daily. This will reduce the risk of hypocalcaemia. Monitoring of serum calcium and phosphate levels is also required. 7, 12 [Level 4]

- Sodium clodronate is an alternative for bone pain in patients with breast cancer and myeloma. 7, 8 [Level 2++] Oral administration is often poorly tolerated. It may be given intravenously or subcutaneously. 5, 13 [Level 4]

- Ibandronic acid is currently only licensed for the management of bone metastases in patients with metastatic breast cancer. It may be administered orally or intravenously. 4, 14 [Level 4]. It may have a better renal profile than zoledronic acid. 15 [Level 2+]

- Patients should be warned of the possibility of a ‘flare’ of bone pain and transient ‘acute phase reactions’ characterized by fever and myalgia which occur in 15-30% of patients. These generally occur after the first infusion of nitrogen containing bisphosphonates and less frequently after following infusions. 6 [Level 4]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route of administration</th>
<th>Diluent</th>
<th>Rate of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic Acid</td>
<td>4mg</td>
<td>Intravenously</td>
<td>100ml sodium chloride 0.9% or dextrose 5%</td>
<td>15-30 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Repeat every 4 weeks</td>
</tr>
<tr>
<td>Disodium Pamidronate</td>
<td>90mg</td>
<td>Intravenously</td>
<td>250-500ml sodium chloride 0.9%</td>
<td>Rate not exceeding 1mg/min</td>
</tr>
<tr>
<td>Ibandronic Acid</td>
<td>6mg</td>
<td>Intravenously</td>
<td>100ml sodium chloride 0.9% or dextrose 5%</td>
<td>15 minutes</td>
</tr>
<tr>
<td></td>
<td>50mg</td>
<td>Orally</td>
<td>Not applicable</td>
<td>Repeated every 4-6 weeks</td>
</tr>
<tr>
<td>Sodium Clodronate</td>
<td>600mg-1500mg</td>
<td>Intravenously</td>
<td>500ml sodium chloride 0.9% or dextrose 5%</td>
<td>Depends on dose. Range 2-4 hours</td>
</tr>
</tbody>
</table>

- If effective, bisphosphonate infusions should be repeated at regular intervals. 4, 7, 13, 14, 16 [Level 4]

- A patient who fails to respond to the first dose of a bisphosphonate used for the treatment of pain should, if clinically appropriate, receive a further two consecutive doses at 4-weekly intervals before being considered a non-responder. 7 [Level 2+]

- In patients with disease progression in the skeleton and who are experiencing pains despite the use of oral bisphosphonates or disodium pamidronate, changing to zoledronic acid or ibandronic acid can improve pain control. 6 [Level 2+]

- Since the risk of skeletal related events is continuous, treatment if tolerated should be continued for at least 2 years, even if a patient experiences a bone event. Continuation of treatment beyond 2 years should be based on an individual risk assessment. 6 [Level 4]

- Bisphosphonates should not be discontinued once skeletal events occur (unless for other clinical reasons) as continuing use significantly reduces the risk of subsequent skeletal events. 6 [Level 2+]

- Table 7.1 gives further details of the dosing regimens for the commonly used bisphosphonates.
7.2.2 **Bisphosphonates in renal failure**

- Hypocalcaemia is a well recognised electrolyte abnormality associated with bisphosphonates.
- Renal failure and other electrolyte abnormalities, particularly hypomagnesaemia, frequently coexist with hypocalcaemia. 3 [Level 4]
- To avoid renal toxicity with bisphosphonates, serum creatinine should be checked and hydration status clinically assessed, prior to each treatment. The serum calcium should also be checked prior to every infusion. 6, 17 [Level 4]
- The risk of renal failure is directly related to drug infusion time and dosage. The use of high dose zoledronic acid with a short infusion time is especially nephrotoxic. 3 [Level 4]
- Treatment with zoledronic acid and disodium pamidronate should not be initiated in patients with severe renal impairment (Cr Cl<30mls/min) unless in cases of life-threatening hyperalcaemia where the benefits are judged to outweigh the risks. 7, 12, 16 [Level 4]
- When using bisphosphonates for the treatment of bone pain, and where there is persistent renal deterioration but a need for treatment, it may be appropriate to consider either a dose reduction or a longer infusion time. Close monitoring is essential. 6 [Level 4]
- There is a growing body of evidence showing that ibandronic acid is better tolerated in renal failure compared to other bisphosphonates. 24 [Level 2+] However, dose reduction, monitoring, and longer infusion times are still required if there is severe renal impairment. 20 [Level 4]
- Table 7.2 gives details of the bisphosphonate dose adjustments required in renal impairment.

7.2.3 **Osteonecrosis of the jaw (ONJ)**

- Osteonecrosis of the jaw has been reported in cancer patients whose treatment regimens include intravenous bisphosphonates. A very small number of cases have also been reported in patients receiving oral bisphosphonates for non-cancer indications. Clinical features include exposed bone in the maxillofacial area, which occurs in association with dental surgery or can occur spontaneously, with no evidence of healing. 19, 20, 21 [Level 4]
- A working diagnosis is made when there is no evidence of healing after 6 weeks of appropriate evaluation and dental care and no evidence of metastatic disease in the jaw or osteoradionecrosis. If osteonecrosis does occur, invasive dental procedures should be avoided if possible. 19 [Level 4]
- Where clinically appropriate, patients should have a dental examination and any dental treatment required before starting bisphosphonate treatment. 3-5, 7, 13, 14, 16, 19 [Level 4]
- Patients should be educated regarding the importance of good oral hygiene to reduce the risk of dental infection and periodontal infections. They should be encouraged to advise their dentist they are receiving bisphosphonate treatment. 19 [Level 4]
- Length of exposure to bisphosphonates is strongly associated with development of ONJ. It is extremely rare for those patients receiving less than 12 treatments to develop ONJ. Therefore if a patient has a poor prognosis and it is anticipated that they are only going to receive a few infusions for bone pain, dental checks may not be essential or appropriate. 19 [Level 4]
- Written information regarding bisphosphonate therapy and preventative measures for ONJ should be made available to patients. 22 [Level 4]
- In patients who develop ONJ whilst receiving bisphosphonates, the decision to stop or continue treatment should be made on a case by case basis. Cessation of therapy may not have an effect on established osteonecrosis. Referral to the local dental hospital, an oral surgeon or dental oncologist should be considered for further management. 6, 19 [Level 4]
- Patients receiving bisphosphonates and who have dental problems other than ONJ should receive the least invasive dental treatment. 6 [Level 4]
Table 7.2 Dosage adjustments for use of bisphosphonates in patients with impaired renal function 4, 5, 7, 12, 13, 14, 16, 18 [Level 4]

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Zoledronic Acid</th>
<th>Disodium Pamidronate</th>
<th>Intravenous Ibandronic Acid</th>
<th>Oral Ibandronic Acid</th>
<th>Intravenous Sodium Clodronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>4mg</td>
<td>90mg over 4-6 hours.</td>
<td>6mg over 15 minutes.</td>
<td>50mg daily.</td>
<td>600-1500mg.</td>
</tr>
<tr>
<td>50-60</td>
<td>3.5mg</td>
<td>90mg over 4-6 hours.</td>
<td>6mg over 1 hour.</td>
<td>50mg daily.</td>
<td>25% dose reduction recommended.</td>
</tr>
<tr>
<td>40-49</td>
<td>3.3mg</td>
<td>90mg over 4-6 hours.</td>
<td>6mg over 1 hour.</td>
<td>50mg daily.</td>
<td>25-50% dose reduction recommended.</td>
</tr>
<tr>
<td>30-39</td>
<td>3.0mg</td>
<td>90mg over 4-6 hours.</td>
<td>6mg over 1 hour.</td>
<td>50mg daily.</td>
<td>25-50% dose reduction recommended.</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Not recommended unless benefit outweighs risk.</td>
<td>Not recommended unless benefit outweighs risk.</td>
<td>2mg over 1 hour.</td>
<td>50mg weekly.</td>
<td>Not recommended especially with creatinine clearance &lt;10ml/min.</td>
</tr>
</tbody>
</table>

7.3 **STANDARDS**

1. Treatment with opioids and non-steroidal anti-inflammatory agents should be optimised before using bisphosphonates for malignant bone pain. 7 [Grade D]

2. The use of bisphosphonates for the management of malignant bone pain should be clearly documented in the case notes. 22 [Grade D]

3. Subsequent infusions of the bisphosphonate should be given as per the recommended regimen for each drug. 4, 5, 7, 13, 14, 16, 18 [Grade D]

4. A patient who fails to respond to the first dose of a bisphosphonate used for the treatment of pain, should, if clinically appropriate, receive a further two consecutive doses at 4-weekly intervals before being considered a non responder. 7 [Grade B]

5. The serum creatinine and adjusted calcium should be checked prior to each bisphosphonate infusion. 6, 17 [Grade B]

6. Those patients prescribed zoledronic acid should also have calcium and vitamin D supplements prescribed. 12 [Grade D]

7. Patient Information Sheets on the use of bisphosphonates and potential adverse effects should be provided. 22 [Grade D]
7.4 REFERENCES


### 7.5 CONTRIBUTORS

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<td>Wirral</td>
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<tr>
<td>Clatterbridge Centre for Oncology NHS Foundation Trust</td>
<td></td>
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<tr>
<td>Wirral</td>
<td></td>
</tr>
</tbody>
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