New Medicine Assessment

Ibandronic Acid 50 mg Tablets (Bondronat®)

for the adjuvant treatment of early breast cancer in postmenopausal women with a high risk of recurrence (unlicensed indication)

Recommendation: Amber 0

- Suitable for prescribing in primary care following recommendation or initiation by a specialist.
- Little or no specific monitoring required.
- Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.
- Brief prescribing document or information sheet may be required.

Primary care prescribers must be familiar with the drug to take on prescribing responsibility or must get the required information.

When recommending or handing over care, specialists should ask primary care prescribers to take over prescribing responsibility, and should give enough information about the indication, dose, monitoring requirements, use outside product licence and any necessary dose adjustments to allow them to confidently prescribe.

Summary of supporting evidence:

- NICE recommends offering bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy to postmenopausal women with node-positive invasive breast cancer or considering bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy for postmenopausal women with node-negative invasive breast cancer and a high risk of recurrence. [1]
- The European Society of Medical Oncology (ESMO) recommends bisphosphonates for early breast cancer in women with low-oestrogen status (undergoing ovarian function suppression or postmenopausal), especially if at high risk of relapse. The recommendations do not specify which bisphosphate to use. [2]
- The American Society of Clinical Oncology (ASCO) lists ibandronic acid among the bisphosphonates it recommends for adjuvant therapy in breast cancer. [3]
- Authors of a meta-analysis of 18,766 women concluded that adjuvant bisphosphonates reduce the rate of breast cancer recurrence in the bone and improve breast cancer survival, but benefit is most apparent in women who were postmenopausal when treatment began. [4]
- An RCT comparing different bisphosphonates including zoledronic acid and ibandronic acid in 6097 patients demonstrated no evidence of differences in efficacy by type of bisphosphonate, either in overall analysis or subgroups.
- Ibandronic acid is listed as a treatment option by The Christie NHS Foundation Trust who have produced a patient information leaflet to support its use.
- Using oral ibandronate would release capacity on chemotherapy units and save the

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patient having to attend hospital.
- Ibandronic acid provides an alternative treatment option for patients where there are venous access issues or renal insufficiency.

Details of Review

Name of medicine (generic & brand name)**:**

Ibandronic Acid (Bondronat®)

Strength(s) and form(s):

50mg tablets

Dose and administration:

One 50 mg film-coated tablet daily.

BNF therapeutic class / mode of action:

Bisphosphonates/osteoclast inhibitors

Licensed indication(s)

Bondronat is indicated in adults for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. [5]

Proposed use (if different from, or in addition to, licensed indication above):

Adjuvant treatment of early breast cancer in postmenopausal women with a high risk of recurrence (unlicensed indication).

Course and cost:

Bondronat 50 mg tablets X 28 = £83.14 (May 2023 Electronic Drug Tariff) [6]

Annual cost per patient = £1,083

Current standard of care/comparator therapies:

- Zoledronic acid 4 mg infusion: Cost to deliver simple parenteral chemotherapy at first attendance £161 (2022-23 National tariff price), price per dose £4.83 (Electronic market information tool), administered 6 monthly, Annual cost = £331.66. [7]

Relevant NICE guidance:

NICE guideline (NG101) Early and locally advanced breast cancer: diagnosis and management [1]

1.9.1 Offer bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy to postmenopausal women with node-positive invasive breast cancer. [2018]

1.9.2 Consider bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy for postmenopausal women with node-negative invasive breast cancer and a high risk of

recurrence. Risk can be estimated using a range of standardised tools and clinical expertise. [2018]

1.9.3 Discuss the benefits and risks of bisphosphonate treatment with women, particularly the risk of osteonecrosis of the jaw, atypical femoral fractures and osteonecrosis of the external auditory canal. Follow the Medicines and Healthcare products Regulatory Agency/Commission on Human Medicines (MHRA/CHM) advice on bisphosphonates. [2018]

Background and context

In 2018, NICE concluded that there was good evidence that treatment with sodium clodronate and zoledronic acid improved disease-free and overall survival in postmenopausal women with node-positive invasive breast cancer. [1] The European Society of Medical Oncology (ESMO) has produced clinical practice guidelines recommending Bisphosphonates for early breast cancer in women with low-oestrogen status (undergoing ovarian function suppression (OFS) or postmenopausal), especially if at high risk of relapse. [2] The American Society of Clinical Oncology (ASCO) also produced guidance for the use of adjuvant bisphosphonates in breast cancer. ASCO support bisphosphonate use early in breast cancer in post-menopausal women and included oral ibandronate 50 mg daily as a therapeutic option. [3]

Ibandronic acid for the adjuvant treatment of early breast cancer in postmenopausal women with a high risk of recurrence was prioritised for review following a request from Lancashire Teaching Hospitals.

Summary of evidence

Summary of efficacy data in proposed use:

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [4]

This meta-analysis used data from 26 randomised controlled trials comprising data from 18,766 participants (18,206 of these patients in trials of 2-5 years of bisphosphonate). Trials were eligible if they began before 2008 and randomly assigned women between a bisphosphonate of any type, dose, and schedule versus a control group (open label or placebo) with no bisphosphonate, all other treatments being similar in both groups. Information was sought during 2012–14 for each individual patient on date of randomisation, allocated treatment, age, menopausal status, tumour diameter, grade, spread to locoregional lymph nodes, HER2 and oestrogen and progesterone receptor (ER/PR) status, dates and sites of any breast cancer recurrence, other second primary cancer, bone fracture, and the date and cause of death. The pre-defined coprimary endpoints were any recurrence of breast cancer (distant, locoregional, or new primary in the contralateral breast); distant recurrence, ignoring any previous locoregional or contralateral recurrence; and breast cancer mortality.

Overall, the reductions in recurrence (RR 0·94, 95% CI 0·87–1·01; 2p=0·08), distant recurrence (0·92, 95% CI 0·85–0·99; 2p=0·03), and breast cancer mortality (0·91, 95% CI 0·83–0·99; 2p=0·04) were of only borderline significance, but the reduction in bone recurrence was more definite (0·83, 95% CI 0·73–0·94; 2p=0·004). Among premenopausal women, treatment had no apparent effect on any outcome, but among 11,767 postmenopausal women it produced highly significant reductions in recurrence (RR 0·86, 95% CI 0·78–0·94; 2p=0·002), distant recurrence (0·82, 95% CI 0·74–0·92; 2p=0·0003), bone recurrence (0·72, 95% CI 0·60–0·86; 2p=0·0002), and breast cancer mortality (0·82, 95% CI 0·73–0·93; 2p=0·002). Even for bone recurrence, however, the heterogeneity of benefit was barely significant by menopausal status (2p=0·06 for trend with menopausal status) or age (2p=0·03), and it was non-significant by bisphosphonate class, treatment schedule, oestrogen receptor status, nodes, tumour grade, or concomitant chemotherapy. No differences were seen in non-breast cancer mortality. Bone fractures were reduced (RR 0·85, 95% CI 0·75–0·97; 2p=0·02).

The authors did caution that additional studies will provide more reliable comparisons for different bisphosphonate regimens.

J Gralow et el Randomised controlled trial [8]

This RCT was an open-label randomized design with equal probability of receiving one of three bisphosphonate treatments for 3 years: (arm 1: ZA) intravenous zoledronic acid (monthly for 6

months, then every 3 months); (arm 2: CLOD) oral clodronate (1600mg daily); or (arm 3: IBAN) oral ibandronate (50mg daily). The study enrolled female patients with pathologic stage I–III breast cancer following surgery. Patients must have received, or have been planning to receive, systemic adjuvant therapy. Neoadjuvant therapy was permitted if enrolled after surgery. Radiation therapy was allowed at any time. Patients with previous bisphosphonate treatment for bone density were eligible if discontinued at registration. Other requirements were age 18 years and older, adequate local therapy, serum creatinine no more than 2 Institutional Upper Limit of Normal and calculated creatinine clearance no less than 30 ml/min, dental examination within 6 months of study initiation, and negative pregnancy test in women with reproductive potential. Patients with renal failure or history of prior malignancy (other than specified in situ cancers or other cancers from which they were disease free for ≥ 5 years) were excluded from participation. The primary outcome was disease-free survival (DFS), defined as time from registration to first occurrence of disease recurrence (local, regional, distant), new breast primary, or death from any cause.

DFS did not differ across arms in a log-rank test (P= 0.49); 5-year DFS was 88.3% (zoledronic acid: CI95% = 86.9% to 89.6%), 87.6% (clodronate: CI95% = 86.1% to 88.9%), and 87.4% (ibandronate: CI95% = 85.6% to 88.9%). Additionally, 5-year overall survival did not differ between arms (log rank P= 0.50) and was 92.6% (zoledronic acid: CI95% = 91.4% to 93.6%), 92.4% (clodronate: CI95% 91.2% to 93.5%), and 92.9% (ibandronate: CI95% = 91.5% to 94.1%).

Summary of safety data:

Ibandronic acid has contraindications in the following scenarios:

- Hypersensitivity to ibandronic acid or to any of its excipients.
- Hypocalcaemia.
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 60 minutes. [5]

The SPC also lists the following special warnings and precautions:

- Orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. The risk of severe oesophageal adverse experiences appears to be greater in patients who do not comply with the dosing instruction.
- Osteonecrosis of the jaw (ONJ) has been reported very rarely in the post marketing setting in patients receiving Bondronat® for oncology indications.
- Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy.
- Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis.
- Since Acetylsalicylic acid, Nonsteroidal Anti-Inflammatory medicinal products (NSAIDs) and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration. [5]

A list of adverse reactions from the SPC for Bondronat® is tabulated below;

Table 1 - Adverse Drug Reactions Reported for Oral Administration of Bondronat®

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to < 1/100)	Rare (≥1/10,000 to <1/1000)	Very rare (<1/10,000)	Not known
Blood and lymphatic system disorders		Anaemia			

Immune system disorders				Hypersensitivity, bronchospasm, angioedema, Anaphylactic reaction/shock	Asthma exacerbation
Metabolism and nutrition disorders	Hypocalcaemia				
Nervous system disorders		Paraesthesia, dysgeusia (taste perversion)			
Eye disorders			Ocular inflammation		
Gastrointestinal disorders	Oesophagitis, abdominal pain, dyspepsia, nausea	Haemorrage, duodenal ulcer, gastritis, dysphagia, dry mouth			
Skin and subcutaneous tissue disorders		Pruritus		Stevens-Johnson Syndrome, Erythema Multiforme, Dermatitis Bullous	
Musculoskeletal and connective tissue disorders			Atypical subtrochanteric and diaphyseal femoral fractures	Osteonecrosis of jaw Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)	
Renal and urinary disorders		Azotaemia (uraemia)			
General disorders and administration site conditions	Asthenia	Chest pain, influenza-like illness, malaise, pain			
Investigations		Blood parathyroid hormone increased			

Strengths and limitations of the evidence:

Strengths

- NICE recommends offering bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy to postmenopausal women with node-positive invasive breast cancer or considering bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy for postmenopausal women with node-negative invasive breast cancer and a high risk of recurrence. [1]
- The European Society of Medical Oncology (ESMO) recommends bisphosphonates for early breast cancer in women with low-oestrogen status (undergoing OFS or postmenopausal), especially if at high risk of relapse. The recommendations due not specify which bisphosphate to use. [2]
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- Ibandronic acid is listed as a treatment option by The Christie NHS Foundation Trust who have produced a patient information leaflet to support its use. [9]
- Using oral ibandronate would release capacity on chemotherapy units and save the patient having to attend hospital.

- Ibandronic acid provides an alternative treatment option for patients where there are venous access issues or renal insufficiency.

Limitations

- NICE omits ibandronic acid from its recommendations relating to adjuvant bisphosphonate therapy in breast cancer.
- The Clatterbridge Cancer Centre predominantly uses zoledronic acid in the treatment of early breast cancer. There are no resources for the use of ibandronic acid and it is believed that ibandronic acid is not used in this indication in the Trust.
- There is a larger body of evidence supporting the use of zoledronic acid and sodium clodronate.
- Ibandronic acid is more expensive per year than zoledronic acid.

Prescribing and risk management issues:

Ibandronic acid 50 mg tablets should only be initiated by physicians experienced in the treatment of cancer.

Ibandronic acid 50 mg tablets should be taken after an overnight fast (at least 6 hours) and before the first food or drink of the day. Medicinal products and supplements (including calcium) should similarly be avoided prior to taking Ibandronic acid 50 mg tablets. Fasting should be continued for at least 30 minutes after taking the tablet. Water may be taken at any time during the course of Ibandronic acid 50 mg treatment.

Water with a high concentration of calcium should not be used. If there is concern regarding potentially high levels of calcium in the tap water (hard water), it is advised to use bottled water with a low mineral content.

- The tablets should be swallowed whole with a full glass of water (180 to 240 ml) while the patient is standing or sitting in an upright position.

- Patients should not lie down for 60 minutes after taking Ibandronic acid 50 mg.

- Patients should not chew, suck or crush the tablet because of a potential for oropharyngeal ulceration.

- Water is the only drink that should be taken with Ibandronic acid 50 mg.

Commissioning considerations:

Innovation, need and equity implications of the intervention:
Ibandronic acid provides an alternative treatment option for patients where there are venous access issues or renal insufficiency.
Financial implications of the intervention:
Lancashire Teaching Hospitals state that there are approximately 400 patients currently receiving zoledronic acid. It is anticipated that many patients will not want/be able to comply with the requirements of taking an oral bisphosphonate. It is estimated that approximately 10% of patients would prefer to use oral bisphosphonates (40 patients). To treat a patient with zoledronic acid infusion 6 monthly would cost £332 annually. To treat a patient annually with oral daily ibandronate 50 mg is £1,083. The cost difference to treat one patient with oral ibandronate rather than zoledronic acid is £751.

Total anticipated additional annual cost to the ICB: 40 X £751 = **£30,040**
Service Impact Issues Identified:
Currently, patients attend the chemotherapy unit to receive IV zoledronic acid, which takes up time for the unit and the patient so using oral ibandronate would release capacity on the unit and save the patient having to attend hospital.
Equality and Inclusion Issues Identified:
None identified.
Cross Border Issues Identified:
Neither GMMMG nor Pan Mersey APC have a position for unlicensed use of ibandronic acid.
Legal Issues Identified:
N/A
Media/ Public Interest:
N/A

References

[1] National Institute for Health and Care Excellence, "Early and locally advanced breast cancer: diagnosis and management," July 2018. [Online]. Available: https://www.nice.org.uk/guidance/ng101. [Accessed May 2023].

[2] F Cardoso et al, "Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up," *Annals of Oncology,* vol. 30, pp. 1194-1220, June 2019.

[3] A Eisen et al, "Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: ASCO-OH (CCO) Guideline Update," *J Clin Oncol,* vol. 40, no. 7, pp. 787-800, 2022.

[4] Early Breast Cancer Trialists' Group (EBCTCG), "Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials," *Lancet,* vol. 386, pp. 1353-1361, 2017.

[5] Electronic Medicines Compendium, “Summary of Product Characteristics Bondronat 50 mg tablets,” Jan 2021. [Online]. Available: https://www.medicines.org.uk/emc/product/9373/smpc. [Accessed May 2023].

[6] Business Services Authority, “Drug Tariff,” [Online]. Available: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff. [Accessed 28 June 2023].

[7] DHSC, “Drugs and pharmaceutical electronic market information tool (eMIT),” [Online]. Available: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. [Accessed 28 June 2023].

[8] J Gralow et al , “Phase III Randomized Trial of Bisphosphonates as Adjuvant Therapy in Breast Cancer: S0307,” *JNCI J Natl Cancer Inst,* vol. 112, no. 7, pp. 698-707, 2020.

[9] The Christie NHS Foundation Trust, “Ibandronic acid for metastatic breast,” July 2020. [Online]. Available: https://www.christie.nhs.uk/media/nycihpyt/510-ibandronic-acide-for-metastatic-breast-cancer-ct-unlocked.pdf. [Accessed 28 June 2023].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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