

Prescribing Framework for Ibandronic Acid 50mg tablets in post-menopausal women with breast cancer

Patients Name:..... Unit Number:

Patients Address:.....(Use addressograph sticker)

G.P's Name:.....

Communication

We agree to treat this patient within this Prescribing Framework

Specialist Prescriber's Name..... Prof Reg. No.

Specialist Prescriber's Signature..... Date:.....

Where prescriber is not a consultant:

Consultant's Name: GMC No

Consultant's Signature Date:.....

GP's Signature:..... Date:.....

The front page of this form should be completed by the specialist and the form sent to the patient's general practitioner.

The patient's GP should sign and **send back to specialist**, to confirm agreement to enter into shared care arrangement. If the General Practitioner is **unwilling** to accept prescribing responsibility for the above patient the specialist should be informed within two weeks of receipt of this framework and specialist's letter.

1. Background

This document has been written to support primary care clinicians in the management of post-menopausal women with breast cancer initiated on ibandronic acid 50mg by secondary care specialists to improve breast cancer survival. Ibandronic acid is unlicensed for this indication.

A large collaborative meta-analysis¹ (involving 18,766 women of whom 11,767 were post-menopausal) found that for post-menopausal women with breast cancer adjuvant bisphosphonates reduced the rate of breast cancer recurrence and improved breast cancer survival.

The absolute reduction with bisphosphonate use in post-menopausal women at 10 years was 3.0% for breast cancer recurrence (from 25.8%); 3.4% for distant recurrence (from 21.2%); 2.2% for bone recurrence (from 8.8%); and 3.3% for breast cancer mortality (from 18.0%).

This benefit was only seen with certain bisphosphonates including zoledronic acid IV 6 monthly and oral ibandronic acid 50mg daily. Numbers were insufficient to assess the efficacy of the standard treatments for osteoporosis, oral alendronate and risedronate, for this indication¹.

None of the bisphosphonates are currently licensed for this indication. The 'off licence' use of ibandronic acid 50mg tablets has been approved by the Drug and Therapeutics Committee at Hull and East Yorkshire Hospitals NHS Trust.

There is clinical support for the introduction of bisphosphonates for this cohort of women². It is included in the breast cancer CRG service specification and endorsed as a priority for implementation at the UK Breast Cancer Meeting (UKBCM)³ in November 2015.

This document should be read in conjunction with the guidance "Responsibility for prescribing between Primary & Secondary/Tertiary Care" <https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf>

2. Indication

Post-menopausal women with breast cancer who are assessed by a specialist to be at sufficient risk of breast cancer recurrence.

3. Medication / Dosage / Duration of treatments

The standard dose is ibandronic acid 50mg Once a Day for up to 3 years.

Dose Adjustment

- Elderly population (> 65 years): No dose adjustment is necessary⁴
- Patients with hepatic impairment: No dose adjustment is required⁴
- Patients with renal impairment⁴
 - For patients with mild renal impairment (eGFR/CrCl \geq 50 and < 80 mL/min), no dose adjustment is necessary

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- For patients with moderate renal impairment (eGFR/CrCl \geq 30 and $<$ 50 mL/min) a dose adjustment to one 50mg tablet every second day is recommended
- For patients with severe renal impairment (eGFR/CrCl $<$ 30 mL/min) a dose adjustment to one 50mg tablet once weekly is recommended

Zoledronic acid 4mg IV 6 monthly for 3 years will be offered to patients where chemotherapy is planned and those unable to tolerate ibandronic acid tablets.

NOTE: Many laboratory results are expressed as eGFR. While it is likely that in many cases the eGFR and the CrCl will be very similar, beware that differences could occur in people at extremes of body size.

4. Adverse effects

Full list of side effects / contraindications is given in the Ibandronic Acid 50mg tablets SPC www.emc.medicines.org.uk

Oral bisphosphonates have been associated with dysphagia, oesophagitis and oesophageal or gastric ulcers.

Osteonecrosis of the jaw (MHRA warning):

- Patients should be advised to have a dental examination with appropriate preventative dentistry prior to treatment with bisphosphonates.
- During bisphosphonate treatment, patients should maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling.

Atypical femoral fractures (MHRA warning):

- During bisphosphonate treatment, patients should be advised to report any thigh, hip, or groin pain.
- Any patient who presents with such symptoms should be evaluated for an incomplete femur fracture.

Oesophageal reactions (MHRA warning):

- Patients should be advised to stop taking the tablets and to seek medical attention if they develop any symptoms of oesophageal irritation such as difficulty or pain upon swallowing, chest pain, or new or worsening heartburn.
- See above regarding importance of dosing instructions.

Very rare reports of osteonecrosis of the external auditory canal (MHRA warning):

- Patients should be advised to report any ear pain, discharge from the ear or an ear infection during bisphosphonate treatment.
- Review current medicines:
- Advise patient to stop any other bisphosphonate that they may be taking; for example: risedronate or alendronate.
- For patients taking a regular NSAID consider whether this can be discontinued.

Contraindications: Hypocalcaemia, inability to stand or sit upright for at least 60 minutes, abnormalities of the oesophagus which delay oesophageal emptying such as stricture or

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achalasia and hypersensitivity to the active substance or to any of the excipients (e.g. lactose intolerance).

5. Interactions

Full list of interactions is given in the Ibandronic Acid 50mg tablets SPC (www.emc.medicines.org.uk).

There are no significant drug interactions but products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk and food, are likely to interfere with absorption of ibandronic acid.

Since acetylsalicylic acid, NSAIDs and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration.

6. Monitoring

LFT's U&E's, creatinine, serum calcium, phosphate and magnesium, creatinine clearance every 3 months.

7. Information to patient

- Patients need to be aware that this is an unlicensed indication (**responsibility of specialist**).
- Patients should be advised on how to take the medicines and be referred to the manufacturer's Patient Information Leaflet for full details:
 - Take tablet first thing in the morning after an overnight fast and before the first food or drink of the day and do not eat or take other medicines for 30minutes to 1 hour after taking the tablet.
 - The tablet should be swallowed whole with a full glass of plain water while standing or sitting in an upright position.
 - Patients should not lie down for 60 minutes after taking ibandronate.
 - Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.
 - Plain water is the only drink that should be taken with ibandronate. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
- Patients and carers should be advised to stop tablets and seek medical attention for symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn.
- During treatment patients should maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain or swelling, non-healing sores or discharge to a doctor and dentist.
- Patients should be advised to report any ear pain, discharge from the ear or an ear infection during treatment with a bisphosphonate.
- Patients should be advised to report any thigh, hip, or groin pain during treatment with a bisphosphonate.
- Patients should be advised to contact their GP if they have any concerns with the medication.

8. Responsibilities of clinicians involved

Stage of Treatment	Hospital Specialist	General Practitioner
Initiation	<p>Assessing the patient and establishing a need for bisphosphonate treatment. Discuss rational for treatment and make patient aware of unlicensed indication (not included in PIL). Verbal consent from patient regarding unlicensed use is acceptable and entry on patient's notes. Prescribe initial 28 days' supply. Stop other bisphosphonates. Instruct patient on how to take oral ibandronic acid safely and reliably. Ensure patient can follow administration recommendations. Discuss potential side effects. Baseline blood tests – including renal function and serum calcium. Correct hypocalcaemia if present.</p> <p>All patients should be advised to take supplemental vitamin D 20-25 micrograms (800–1000 units) daily bought over the counter (OTC) from pharmacies, supermarkets or health food shops. If dietary intake of calcium is low, combined calcium and vitamin D preparation can be bought OTC (see more advice on Vitamin D guideline) Include in GP letter whether calcium and vitamin D needs to be prescribed or patient has been advised to buy OTC.</p> <p>Contacting the GP to invite shared care for the patient.</p>	

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<p>Maintenance</p>	<p>Assessing the continued appropriateness for ibandronate on yearly basis. Reviewing any concerns regarding disease progression from the GP within 2 weeks. Ensuring that all other medical professionals in the shared care team are kept informed of any changes in the patient's circumstances.</p>	<p>Providing the patient with repeat prescriptions for ibandronate and calcium supplementation as appropriate for length of time specified by hospital specialist. Stop any repeat prescriptions for other bisphosphonates. For patients taking a regular NSAID review and consider whether this can be discontinued. Monitor LFT's U&E's, creatinine, serum calcium, phosphate and magnesium, creatinine clearance every three months. Annual review including:</p> <ul style="list-style-type: none"> - Blood tests: renal function and serum calcium: - If calcium is out of range or renal impairment becomes severe (eGFR/CrCl < 30 mL/min/1.73m²) discontinue ibandronic acid and contact hospital specialist for advice. - Reduce dose if eGFR/CrCl < 50 mL/min/1.73m² (see 'patients with renal impairment'). - Medication review: to check for compliance; side effects and tolerability; ensure patient and/or carer understands how to administer tablets; check oral hygiene advice is being followed. - Inform the consultant if the patient discontinues treatment for any reason. Any patient not able to comply with dosing instructions or unable to tolerate oral ibandronic acid can be offered zoledronic acid IV as an alternative. - To report any serious adverse reaction to the CSM and the referring consultant. <p>No routine monitoring of toxicity is required, however referral to secondary care is necessary if the patient presents with signs of hypo or hypercalcemia, clinical deterioration or reduced renal function:</p> <ol style="list-style-type: none"> a) If normal at baseline then reduction to <50mL/min b) If below normal at baseline and on appropriately modified dose (see page 2) then reduction of >10mL/min from baseline (i.e. if drops from 38 to 28mL/min) <p>Referring for review if there are signs of disease progression. Ensuring that all other medical professionals in the shared care team are kept informed of any changes in the patient's circumstances. Individual patients who require additional serum creatinine and calcium levels monitoring may be identified by the consultant.</p>
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9. References

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1. Early Breast Cancer Trialists' Collaborative Group (2015). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* 386: 1353–61
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2. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel (2016), *Annals of Oncology* 27: 379–390
<http://annonc.oxfordjournals.org/content/27/3/379.full.pdf+html>
3. UK Breast Cancer Meeting (UKBCM). November 2015. Presentations available here: <http://www.ukbcg.org/content.php?id=245g=6/Presentations-2015>
4. Summary of Product Characteristics. Ibandronic Acid 50mg tablets.
www.medicines.org.uk. Accessed July 21
5. BNF July 2016 <https://www.medicinescomplete.com/mc/bnf/current/PHP4671-ibandronic-acid.htm>
6. NICE Medicines Evidence Commentary, November 2015, Early breast cancer: adjuvant bisphosphonate treatment beneficial in post-menopausal women
<http://www.medicinesresources.nhs.uk/GetDocument.aspx?pagelid=802403>

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APPROVAL PROCESS

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Consultation process:	Breast Cancer Network Site Specific Group
Approved by:	MMIG July 2018
Ratified by:	HERPC July 2018, July 21 NLAPC Nov 21
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Summary

Post-menopausal women with breast cancer at sufficient increased risk of recurrence will be offered a bisphosphonate (by the hospital specialist) to reduce their risk of recurrence and mortality from breast cancer*.

Either as zoledronic acid 4mg IV 6 monthly OR ibandronic acid 50mg tablets (one daily) from the start of adjuvant therapy for a period of 3 years.

Where chemotherapy is planned:

Zoledronic acid 4mg IV 6 monthly for 3 years

Where chemotherapy is not planned:

Ibandronic acid 50mg tablets (one daily) for up to 3 years will be offered.

Responsibilities of hospital specialist:

- Discuss rationale for treatment with patient with the explanation that this is an unlicensed indication. Document it on the patient's notes and hand out the "unlicensed and off label PIL" <https://www.hey.nhs.uk/wp/wp-content/uploads/2016/03/unlicensedOffLabelMedicines.pdf>
- Side effects to be discussed, including osteonecrosis of the jaw (dental examination advised prior to treatment) and atypical femoral fracture. Patients need to be able to comply with dosing instructions.
- Responsible for starting ibandronic acid 50mg (one daily); minimum 28 day script will be supplied.
- Request GP to continue prescribing ibandronic acid for up to 3 years

Responsibilities of primary care clinician:

- Prescribe ibandronic acid 50mg tablets (one daily) as per specialist letter for 3 years in total
- Ensure any other bisphosphonate e.g. weekly alendronate or risedronate is stopped whilst patient is taking ibandronic acid or having IV zoledronic acid.
- Review current NSAID use (increased risk of GI side effects).
- LFT's U&E's, creatinine, serum calcium, phosphate and magnesium, creatinine clearance every 3 months
- **Annual review by GP to include:**
Medication review to check compliance; potential side effects; tolerability of ibandronic acid; ensure patient and/or carer understands how to administer tablets; check oral hygiene advice is being followed.

Ibandronic acid not tolerated or patient is unable to comply with dosing instructions:

Refer back to specialist (zoledronic acid IV 6 monthly will be offered as alternative to make up 3 years).

