THE SHEFFIELD AREA PRESCRIBING GROUP

Prescribing Guidance

For

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

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

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 weekly for 3 cycles; after which ibandronic acid 50mg tablets (one daily) will be offered and initiated by specialist team from 6-36 months.

Where chemotherapy is not planned: Ibandronic acid 50mg tablets (one daily) for 36 months will be offered.

Responsibilities of hospital specialist:

- Discuss rationale for treatment with patient with the explanation that this is an unlicensed indication.
- 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:
  - **30 months (after 3 cycles of zoledronic acid IV infusions during chemotherapy)**
  - **Up to 3 years (no previous zoledronic acid IV Infusion)**
- Patients are followed up at 2-3 years and 5 years from completion of initial adjuvant therapy.

Responsibilities of primary care clinician:

- Prescribe ibandronic acid 50mg tablets (one daily) as per specialist letter (length of time stated on letter).
- 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).
- **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.
  - Annual blood tests: **renal function and serum calcium**

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).
Inform consultant if ibandronic acid is discontinued for any reason.

**See appendix 1*

This is guidance on the management of a condition not a commissioning arrangement

Statement of Purpose

This guidance 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.

Introduction

A large collaborative meta-analysis[1] (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 indication[1].

None of the bisphosphonates are currently licensed for this indication. The 'off licence' use of ibandronic acid 50mg tablets has been approved by the Medicines Safety Committee at Sheffield Teaching Hospitals.

There is clinical support for the introduction of bisphosphonates for this cohort of women[2.] 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.

Indication / patient group

Post-menopausal women with breast cancer who are assessed by a specialist to be at sufficient risk of breast cancer recurrence (*see appendix 1*).

Medication / Dosage / Duration of treatments

The hospital specialist will arrange the first prescription for ibandronic acid 50mg daily (**minimum of 28 days will be supplied**) and will request on-going prescribing by the GP. The specialist will specify the length of treatment (up to 3 years).

Elderly population (> 65 years): No dose adjustment is necessary[4]

Patients with hepatic impairment: No dose adjustment is required[4]

Patients with renal impairment[4]

- No dose adjustment is necessary for patients with mild renal impairment (CrCl ≥ 50 and < 80 mL/min)
- For patients with moderate renal impairment (CrCl ≥ 30 and < 50 mL/min) a dose adjustment to one 50mg tablet every second day is recommended
- For patients with severe renal impairment (CrCl < 30 mL/min) a dose adjustment to one 50mg tablet once weekly is recommended

Creatinine clearance (CrCl) in this document may be approximated to eGFR[5] in primary care for patients with a BMI between 18.5 and 30kg/m^2. The values remain the same but the units become mL/min/1.73m^2.

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Responsibilities of hospital specialist

- Discuss rational for treatment and make patient aware of unlicensed indication
    - Indication is not included in patient information leaflet for ibandronic acid 50mg tablets.
    - Verbal consent from patient regarding unlicensed use is acceptable.
- Instruct patient on how to take oral ibandronic acid safely and reliably (fasting, early morning, upright, swallowed whole with at least 200 ml of water etc). Ensure patient can follow administration recommendations. See 'information for patients' page 6.
- Baseline blood tests – including renal function and serum calcium.
- Adequate intake of calcium and vitamin D is important in all patients:
    - All patients should be advised to take supplemental vitamin D 20-25 micrograms (800–1,000 IU) daily; brought over the counter (OTC) from pharmacies, supermarkets or health food shops.
    - If dietary intake of calcium is low, prescribe combined calcium and vitamin D preparation.
    - Include in GP letter whether calcium and vitamin D needs to be prescribed or patient has been advised to buy vitamin D.
- Discuss potential side effects including:

  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.

Responsibilities of the primary care clinician – see next page

Responsibilities of the primary care clinician

- Issue on-going prescriptions for ibandronic acid 50mg daily for length of time specified by hospital specialist (consider adding stop date to dosing instructions). Ensure other bisphosphonates are stopped during this period.
- For patients taking a regular NSAID review and consider whether this can be discontinued.
- **Annual review including**:
    - Blood tests: renal function and serum calcium:
        - If calcium is out of range or renal function becomes severe (eGFR < 30 mL/min/1.73m^2) discontinue ibandronic acid and contact hospital specialist for advice.
        - Reduce dose if eGFR < 50 mL/min/1.73m^2 (see page 3 '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 CHM and the referring consultant.

Follow up

Patients are routinely seen by the specialist twice during 5 year follow-up; once between 2-3 years and at 5 years post completion of initial adjuvant treatment (surgery +/- chemotherapy +/- radiotherapy).

Side effects / Contraindications

Full list of side effects / contraindications is given in the Ibandronic Acid 50mg tablets SPC (summary of product characteristics) available from www.emc.medicines.org.uk .

Contraindications:

- Hypocalcaemia. This needs to be corrected before the start of treatment and will be checked by the hospital specialist.
- Inability to stand or sit upright for at least 60 minutes.
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.
- Hypersensitivity to the active substance or to any of the excipients (e.g. lactose intolerance).

Special warnings and precautions for use:

- The risk of severe oesophageal adverse experiences appears to be greater in patients who do not comply with the dosing instruction
- Use with caution in patients with active or recent upper gastrointestinal problems
- MHRA/CHM advice: Bisphosphonates use and safety (December 2014)*
- MHRA/CHM advice: Bisphosphonates: atypical femoral fractures (June 2011)*
- MHRA/CHM advice: Bisphosphonates: osteonecrosis of the jaw (November 2009)*
- MHRA/CHM advice: Bisphosphonates: very rare reports of osteonecrosis of the external auditory canal (December 2015)*

See 'Information for patients' page 6

Interactions

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

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

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Information for patients

- 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. 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.

Useful links / Additional information

GMC guidance on prescribing unlicensed medicines is available here:
http://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

NICE

There is no NICE guidance but NICE has published a Medicines Evidence Commentary[6]

References

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 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60908-4/abstract
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 2016
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?pageId=802403

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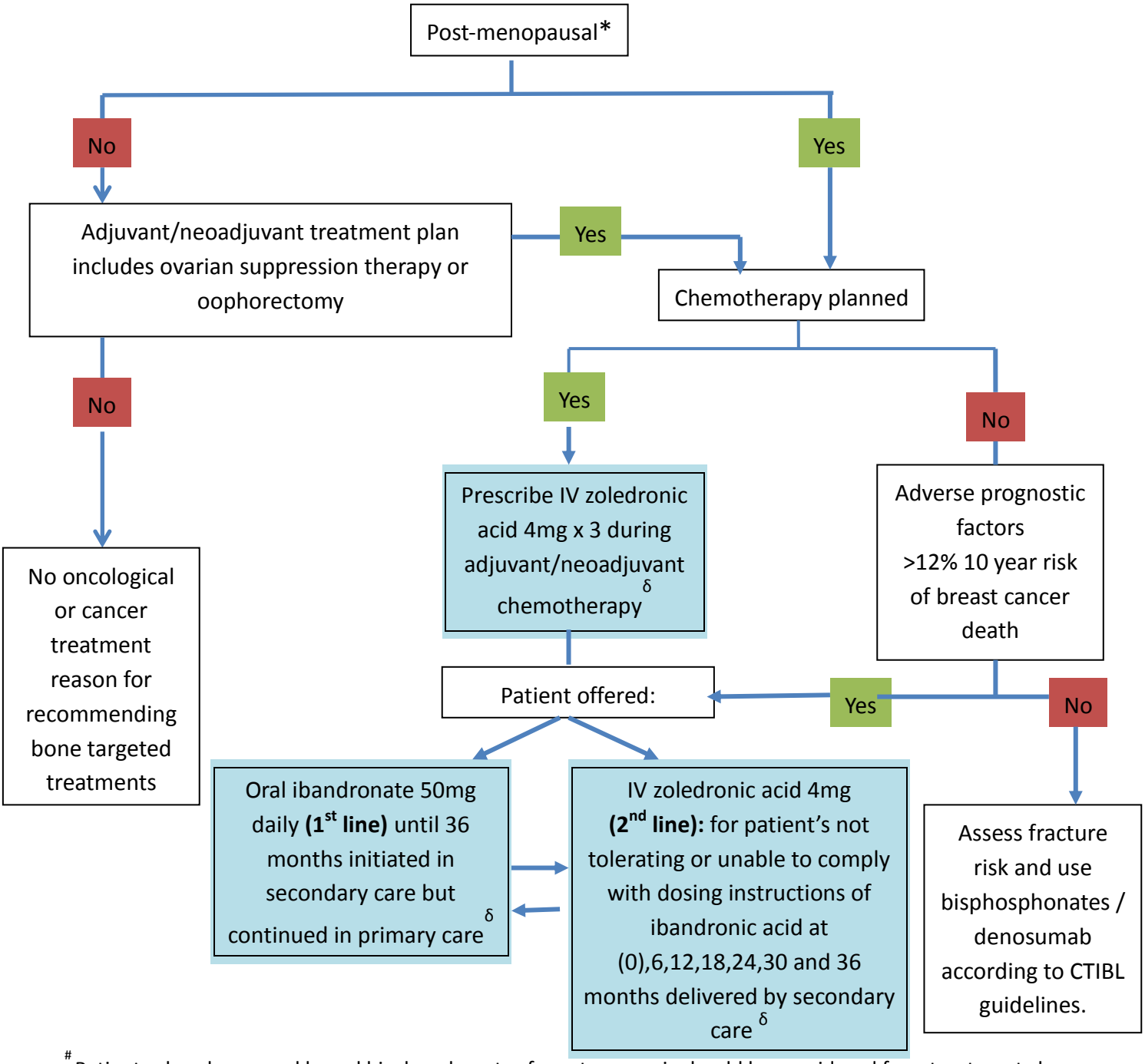
Appendix 1: Selection of patients suitable for adjuvant bisphosphonates[#]



[#] Patients already on weekly oral bisphosphonates for osteoporosis should be considered for a treatment change and follow algorithm

* If not clinically assessable i.e. hysterectomy/IUD then ensure age >55 +/or serum FSH is in post-menopausal range (patient must not be receiving concurrent therapies that can affect the HPG axis)

δ Include vitamin D 800-1000IU daily (+calcium 1000mg daily if low calcium diet)

CTIBL: Cancer Therapy Induced Bone Loss

IV: Intravenous

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