Portsmouth and South East Hampshire Area Prescribing Committee

Shared Care Agreement

Adjuvant Bisphosphonates for Early Breast Cancer

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Authorised by Area Prescribing Committee: February 2017

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This shared care protocol is produced to support the combination of the best of both primary and secondary care for the benefit of the patient. It facilitates seamless transfer of patient treatment from secondary to primary care and provides an information resource to support clinicians providing primary care to the patient.

It supports but does not replace discussion and agreement on an individual patient basis about transfer of care.

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 Formulary and Medicines Committee at Portsmouth Hospitals NHS Trust.

There is clinical support for the introduction of bisphosphonates for this cohort of women.[2] It is included in the NHS England breast cancer CRG service specification and endorsed as a priority for implementation at the UK Breast Cancer Meeting (UKBCM)[3] in November 2015.

Referral Criteria / Indication

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

Dosage

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.

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 greater than or equal to 50 and less than 80 mL/min)
- For patients with moderate renal impairment (CrCl greater than or equal to 30 and less than 50 mL/min) a dose adjustment to one 50mg tablet every second day is recommended
- For patients with severe renal impairment (CrCl less than 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*

Contraindications

- Hypersensitivity to ibandronic acid or any excipients in tablets.
- 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.

Cautions

Osteonecrosis of the jaw

Avoid invasive dental procedures while on bisphosphonate treatment. If invasive dental procedures are unavoidable then stop bisphosphonate for at least 6 weeks prior to the procedure. Treatment can normally resume once bone socket healing has fully occurred. Seek specialist advice if unsure.

Atypical fractures of the femur

Atypical femoral fractures have been reported in patients receiving bisphosphonates. Atypical femoral fractures may occur with little or no trauma in the sub-trochanteric and diaphyseal regions of the femur. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit-risk assessment. During bisphosphonate treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.

Hospital Specialist Responsibilities
Summary

- Discuss rationale 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 200ml of water etc.). Ensure patient can follow administration recommendations.

- 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 (800-1000 IU) daily, which may be bought over the counter (OTC) from pharmacies, supermarkets or health food shops or prescribed by the GP.
    - If dietary intake of calcium is low, prescribe a 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 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. Occasional use of a mild NSAID such as ibuprofen is ok.

Primary Care Clinician Responsibilities
Summary

- 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. Occasional use of a mild NSAID such as ibuprofen should not cause a problem.

Annual Review including:

- Blood tests: renal function and serum calcium
- If calcium is out-of-range or renal impairment becomes severe (eGFR less than 30ml/min/1.73m2) discontinue ibandronic acid and contact hospital specialist for advice.

- Reduce dose if eGFR less than 50ml/min/1.73m2 (see page 2 for information on dosing in 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.

Follow up
Patients are routinely seen by the specialist twice during 5 year follow-up; once between 2-3 years and at 5 years after 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 instructions.
- 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)

Interactions
Full list of interactions is given in the ibandronic acid 50mg tablets SPC (www.medicines.org.uk).
Since acetylsalicylic acid, NSAIDs and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration.

Information for patients
- Patients need to be aware that this is an unlicensed indication (responsibility of specialist). See Appendix 2.
- Patients should be advised on how to take the medicines and be referred to the manufacturer's patient information leaflet for full details. In addition a specific leaflet has been produced to support this use – See Appendix 2. 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.

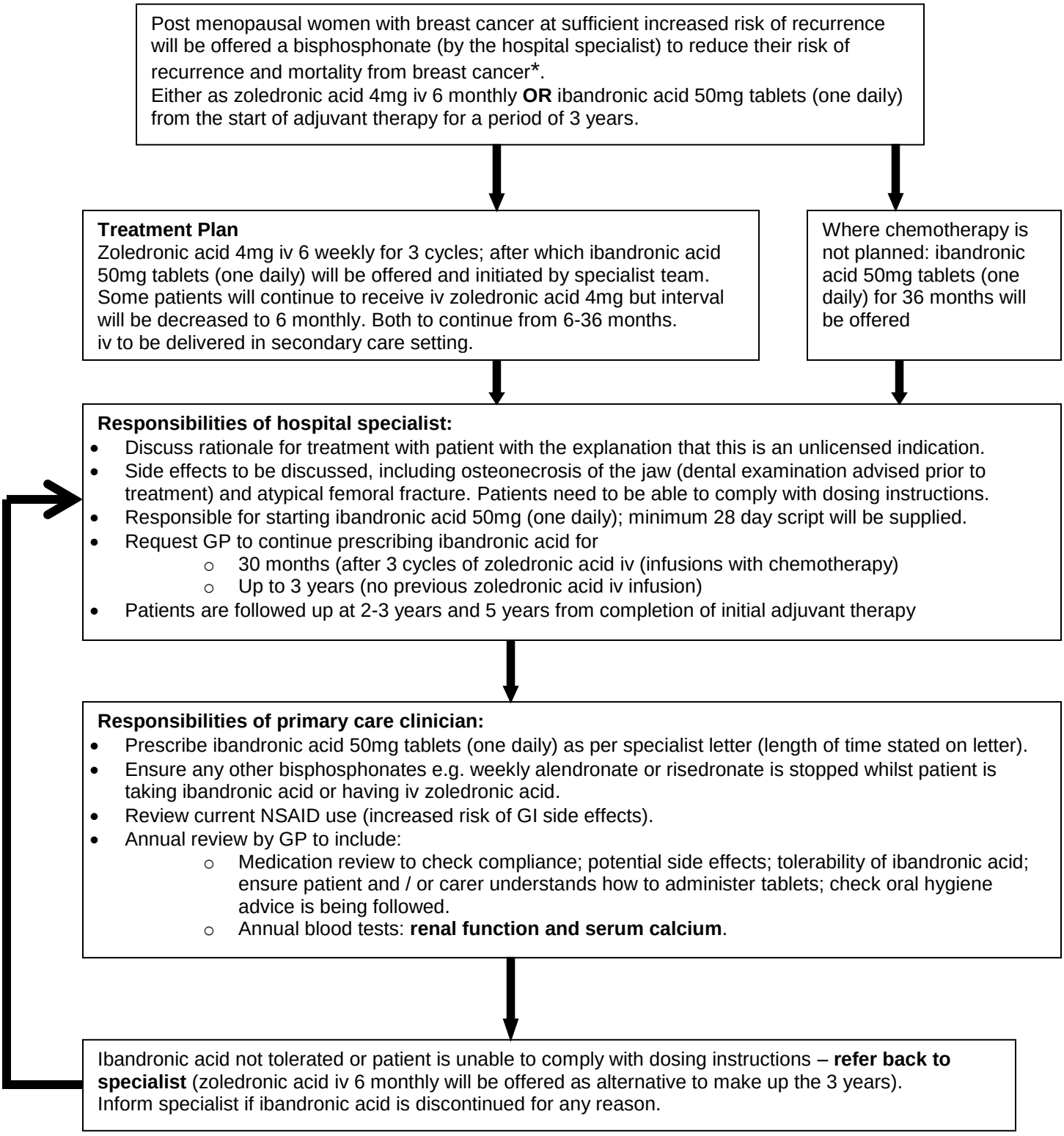
Sources of Information

Name	Role	Telephone Number
Dr Caroline Archer	Consultant Medical Oncologist	via secretary: Linda Morris Tel:023 92 286000 Ext 4790
Catrin Watkinson	Pharmacist (Oncology / Haematology)	Tel: 023 92 886000 Ext 5410
Oncology Pharmacy Office	-	Tel: 023 92 286000 Ext 5424

References

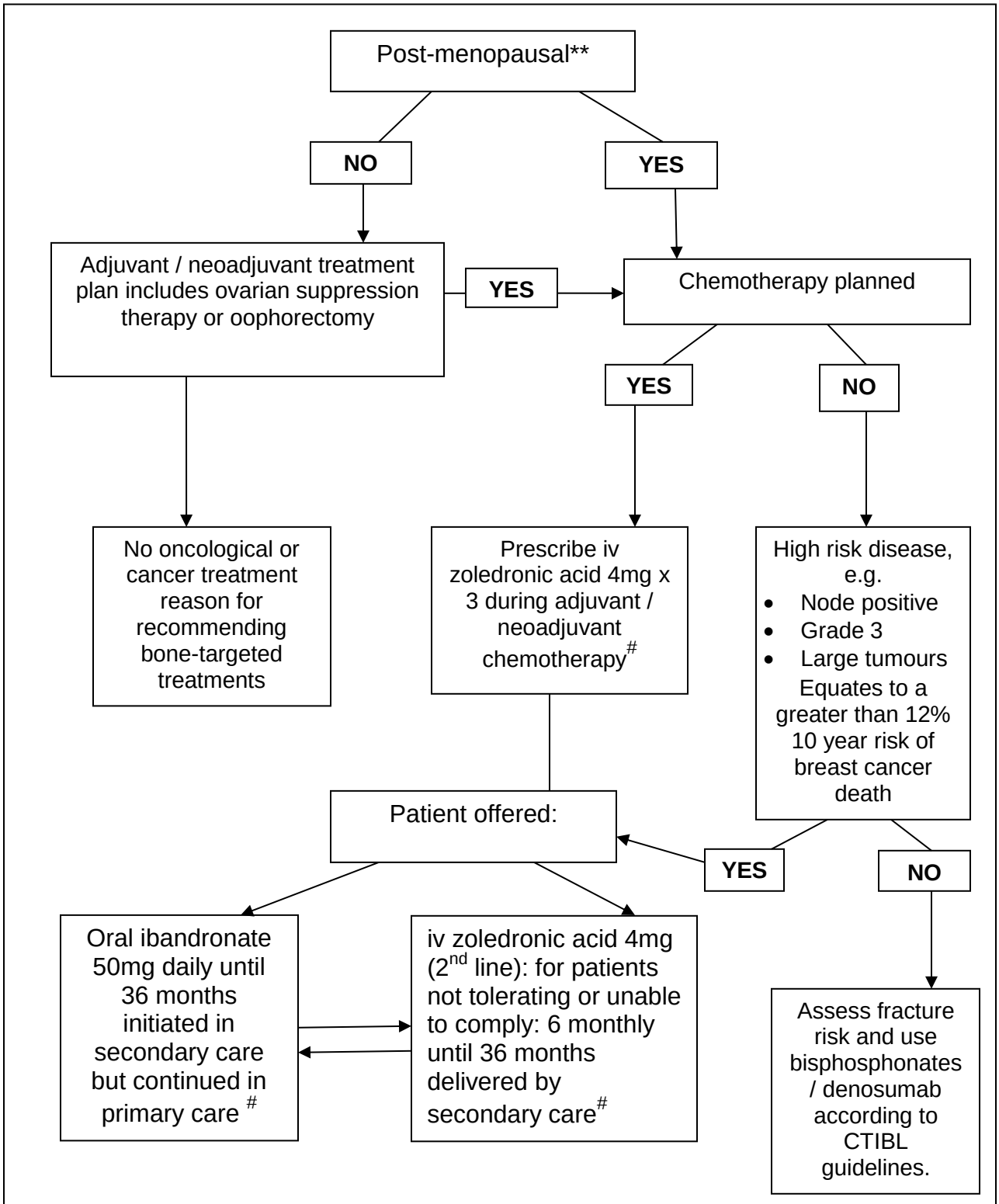
1. Early Breast Cancer Trialists' Collaborative Group (2015). Adjuvant bisphosphonates treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 386:1353-61. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60908-4/abstract
2. Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel (2016), Annals of Oncology 27:379-390. http://annoc.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 December 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.
7. Prescribing Guidance for Ibandronic Acid 50mg tablets in post-menopausal women with breast cancer. The Sheffield Prescribing Group. July 2016.

SUMMARY



* See Appendix 1

Appendix 1: Selection of patients suitable for adjuvant bisphosphonates*



*Patients already on weekly 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)

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

iv intravenous

Portsmouth Hospitals NHS
NHS Trust

Appendix 2

Adjuvant Bisphosphonates for Early Breast Cancer
Information for patients

This leaflet is intended to support you in making decisions about the role of bisphosphonates in your breast cancer care.

What are bisphosphonates?
Bone constantly undergoes a process of renewal. Specialised cells break down old bone and replace it with new bone every day. This process helps to repair damage to the skeleton from everyday activities. We call this process bone turnover. However, as we age this process becomes less efficient and the bones become thinner and weaker.
Bisphosphonates are a group of medications that have been used to treat thin bones (osteoporosis) for many years. Bisphosphonates control the cells that break down bone (osteoclasts) and allow the cells that rebuild bone (osteoblasts) to work better. As a result, they increase bone density and strength and this means that they reduce the risk of bone fractures, especially at the wrist, hip and spine (back bone).

Why are bisphosphonates being used to treat breast cancer?
Clinical studies have shown that breast cancers can recur in bones, often many years after patients have had surgery to remove the cancer from the breast. Doctors think this could be because the chemicals that control bone turnover could also encourage the growth of breast cancer cells inside bones.
Clinical trials of bisphosphonates in early breast cancer started in the 1990's. These drugs were added to standard treatments after breast surgery, like chemotherapy and tamoxifen, and compared to these standard treatments alone. These clinical trials found that bisphosphonates reduced the risk of breast cancer coming back in patients' bones and often meant that patients lived longer.
However not all patients had the same degree of benefit. The greatest benefits from bisphosphonates were seen in two groups of women:

- Post-menopausal women
- Pre-menopausal women who were treated with drugs to suppress their ovaries.

In these groups of women, 1in 3 recurrences of breast cancer in the bone and 1 in 6 deaths from breast cancer at 10 years after diagnosis were prevented.

Who can take bisphosphonates?
Specialists are prescribing this treatment to the following women:

- Post-menopausal women who have had their breast cancer completely removed.
- Pre-menopausal women who are on additional drugs to suppress their ovaries as part of their standard treatment after surgery.

Individuals whose kidneys are not functioning normally will take a reduced dose.
Bisphosphonates are not licensed for use in breast cancer patients to prevent recurrence of the disease, so they must be started by a specialist in hospital who has the appropriate experience. He / she will advise your GP on the recommended treatment and how long you should take the medication for.

How do I take bisphosphonates?
How you take bisphosphonate will depend on whether you are having chemotherapy as part of your treatment plan.
In this case, bisphosphonates will be administered through a drip into a vein using a drug called **zoledronic acid.**

We recommend you take the treatment over 3 years. If you are receiving chemotherapy you will receive 3 doses of zoledronic acid into a vein every 6 weeks at the time you have your chemotherapy injections. This will only add about 15 minutes to the time it takes to give your chemotherapy and should not affect the chemotherapy side-effects you may have.
Once you have finished the chemotherapy you will then have a zoledronic acid infusion at 6, 12, 18, 24, 30 and 36 months. Also, once your chemotherapy is finished you can swap to receiving the treatment orally instead. This can be prescribed by your GP on the advice of a hospital specialist.
For patients who do not require chemotherapy or have finished their treatment instead of intravenous zoledronic acid an oral tablet called Ibandronic acid can be used as an alternative. The dose of this is 50mg once daily. Again, this can be prescribed by your GP on the advice of a hospital specialist.

Ibandronic acid (known as ibandronate) tablets – important things to note

- They must be taken at least 30 minutes before the first food or drink of the day (other than plain tap water). These instructions are important because the drugs will only be effective if taken on an empty stomach.
- Tablets must be swallowed whole and taken with a glass of plain tap water (not less than 200ml or 7 fl oz).
- It is important to stay upright (sitting, standing or walking) for at least 60 minutes after taking the tablet to help it ‘go down properly’.
- It is recommended that it is taken at the same time each day. If you forget to take it on one day it can be taken the following day, do not double up to make up for a forgotten dose.

What side effects might I experience?
Most people will not experience side effects and if they do they usually do not last long. Specific side effects include:

- Flu like symptoms such as fever, aching muscles or headache.

Mild painkillers such as paracetamol or ibuprofen (occasional use), can be taken if needed. Although regular paracetamol is fine to take if you feel you need regular ibuprofen then this must be discussed with your GP.

Oral ibandronate tablets may also cause:

- Nausea
- Inflammation and ulceration of the oesophagus (food pipe)
- Stomach pains

Zoledronic acid only:

- Irregular heartbeats or inflammation in the eye (very rare).

Rare side effects for both oral and intravenous drugs:
There is a link between drugs from the bisphosphonate family and the following rare conditions:

- Osteonecrosis of the jaw is a condition where some cells in the jawbone die. This means that the jaw may also be slow to heal. It is mostly associated with high doses of bisphosphonate drugs and so is unlikely to occur with 6 monthly intravenous treatments. Only a small number

of cases are described worldwide, so the risk with the treatments we are recommending is low (affecting probably less than 1 patient in 100).

- As a precaution, people taking this treatment must have a full dental assessment before they start treatment and get approval from their dentist to receive bisphosphonates. Patients are advised to have regular dental check-ups but should not have non-emergency dental work done 6 weeks before or after an infusion.
- A link to osteonecrosis of the auditory (ear) canal is also reported. This is very rare (fewer than 1 in 10,000 patients). People taking this treatment this treatment are advised to report persistent ear pain and /or discharge from the ear.
- There is also a possible link between taking long term use of bisphosphonate treatment and developing a stress fracture of the thigh bone. This is extremely unlikely to be a problem in the treatment of breast cancer (affecting less than 1 patient in 10,000) as we will be asking you to take the medication for only 3 years in total. If you develop aching pain in the thigh while taking treatment you should let your doctor know.

Is there anything I should look out for while taking bisphosphonates?

As mentioned above some patients experience 'flu-like' symptoms such as fever, aching muscles or headache with the first dose but these usually resolve after the first couple of days and are less likely to occur with subsequent treatments. If symptoms persist, speak to your specialist or GP.

If you experience any of the following symptoms whilst taking this medication you are advised to see your doctor:

- Persistent ear pain and / or discharge from the ear.
- Persistent jaw bone and / or ulceration of the gum.
- Aching pain in the thigh.

Do I need to take extra calcium or vitamin D?

It is recommended that you have an adequate calcium and vitamin D intake whilst on bisphosphonate treatment. Calcium intake should be sufficient if you have a well balanced diet. Two glasses of milk and either a block of cheese (30g portion) or a yoghurt daily should provide an adequate intake of calcium.

For vitamin D you should take a supplement (available from chemists and supermarkets at a recommended dose of 800-1000 IU daily) or as an alternative your GP can prescribe this for you.

Where can I find further information?

This may be obtained from the staff treating you at the hospital or from your GP. Information is also available from the National Osteoporosis Society.

www.nos.org.uk

Helpline: 0808 800 0035 (9.00 am – 5.00 pm Mon-Fri)

Helpline e-mail:nurses@nos.org.uk