North Central London
Joint Formulary Committee

Factsheet

Ibandronic Acid

Adjuvant Breast Cancer Treatment

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For specialists contact details, please click here

Document Control		
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December 2022	V1	Factsheet produced by Dr R Roylance, Dr S Benafif and Ms S Tattersfield; reviewed by NCL ICB (Camden borough team) Agreed by NCL Shared Care Group: 23/12/2022

Disclaimer

Factsheets support GPs in taking ongoing responsibility for continuing a medicine initiated in secondary care. It differs from a shared care agreement where secondary cares retain a proportion of responsibility for ongoing care.

This document is intended for use by healthcare professionals to aid the treatment of patients within NCL. It should not be used for marketing purposes. If you identify information within this document that is inaccurate, please report to admin.ncl-mon@nhs.net.

Ibandronic acid is on the NCL Joint Formulary for the prevention of skeletal events (i.e., pathological fractures or bone complications requiring radiotherapy or surgery) in patients with breast cancer, with or without bone metastases (where denosumab or IV bisphosphonates are not appropriate).

As per local formulary agreement, ibandronic acid is restricted to oncologists and surgeons from the Breast Oncology MDT team and prescribed for patients with breast cancer as part of the adjuvant treatment plan.

The hospital team will:

1. Provide the patient with initial information regarding the treatment and possible adverse effects.
2. Advise the patient to have an assessment with their dentist prior to commencing treatment; initiation will only take place once the specialist team has confirmation from the patient of a dental check and that they are fit to start treatment.
3. Review the patients' baseline blood tests (including renal function and calcium) to determine the appropriate dosage; calcium levels must be adequate before initiating ibandronic acid.
4. Initiate and supply one month of ibandronic acid treatment; inform GP when patient has commenced it so GP can continue prescribing.
5. Initiate calcium and vitamin D supplementation (if indicated) and make an initial one-month supply to avoid delay in treatment. Advise the GP to continue treatment.
6. Counsel the patient on swallowing technique and potential adverse effects; provide information on maintaining good oral hygiene, having routine dental check-ups, and to immediately report any symptoms relating to oesophageal reactions, thigh, hip or groin pain, or oral symptoms.
7. Clinically supervise patient who may either still be having routine follow-ups or be monitored through the stratified follow up programme.

Dose and Administration

The maximum licensed dose is 50mg/day.

Ibandronic acid should be taken on an empty stomach first thing in the morning, swallowed whole with a full glass of plain water while sitting or standing upright; other medications should not be taken for one hour afterwards and the patient should not lie down for one hour afterwards.

A total treatment course of 3 years is indicated for patients with breast cancer.

Calcium and vitamin D supplementation may also be indicated in some patients who do not have adequate oral intake. This should be initiated by the specialist before advising the GP to continue. As supplementation is to avoid drug-induced hypocalcaemia, it can be prescribed on an FP10 prescription (i.e., it is exempt from restrictions on the prescription of vitamins and supplements).

***Renal impairment**:*

- No dose adjustment is necessary for patients with mild renal impairment (Creatinine clearance (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.

***Hepatic impairment**:* No dose adjustment needed.

Discontinuing treatment: Ibandronic acid may be discontinued if patients have persistent side effects leading to intolerance such as dyspepsia. In patients who do not tolerate oral treatment, IV zoledronic acid may be considered. Treatment should be discontinued if patients develop osteonecrosis of the jaw or a fragility fracture.

Adverse Effects

Adverse effect	Frequency	Suggested management by GP
Oesophagitis, dyspepsia, nausea	≥1/100 to <1/10	Ensure patients are taking the tablets correctly as described above. NSAIDs should be avoided in patients taking regular oral bisphosphonates. If not tolerated despite these measures, patient can be referred back to the breast clinic for 6 monthly IV zoledronic acid as an alternative.
Hypocalcaemia	≥1/100 to <1/10	Ensure patient is taking calcium and vitamin D supplementation throughout adjuvant ibandronic acid therapy with the equivalent of 1,000 mg of calcium daily and 800 IU of vitamin D – options include Accrete D3, Evacal D3 or Cacit D3. If the patient has been adherent to calcium and vitamin D supplementation, consider optimising calcium dosage and check adherence. A temporary treatment interruption can be considered to rule out ibandronic acid as the cause.
Osteonecrosis of the jaw (ONJ)	<1/10,000	ONJ is defined as exposed bone, or bone that can be probed through an intraoral or extraoral fistula, in the maxillofacial region that has persisted for >8 weeks in patients with a history of treatment with antiresorptive drugs. (See next section for further information) If a patient reports a new dental issue such as tooth or gum pain, interrupt ibandronic acid until a full dental assessment has been completed and there is confirmation by a dentist that the patient can resume treatment. Treatment should be interrupted for any planned dental procedures and recommencement planned with the input of the patient's dentist. For confirmed ONJ, ibandronic acid should be discontinued indefinitely and the patient should be referred to the ONJ clinic at the Eastman Dental Hospital (part of UCLH) and inform the oncology specialist.
Asthenia		If all other causes have been excluded and it is interfering with quality of life, please contact the oncology team to discuss further.

Healthcare professionals are asked to report any suspected adverse reactions using the Yellow Card Scheme. The above list is not exhaustive; please refer to the summary of product characteristics for further information.

Contraindications

Hypersensitivity to the active substance or to any of the excipients, hypocalcaemia, abnormalities of the oesophagus which delays oesophageal emptying (e.g., stricture or achalasia) or the inability to stand or sit upright for at least 60 minutes.

Special Warnings and Precautions for Use

Patients with disturbances of bone and mineral metabolism

Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting ibandronic acid therapy. Adequate intake of calcium and vitamin D is important in all patients. Patients should receive supplemental calcium and/or vitamin D if dietary intake is inadequate.

Gastrointestinal irritation

Orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when ibandronic acid is given to patients with active upper gastrointestinal problems (e.g. known Barrett's oesophagus, dysphagia, other oesophageal diseases, gastritis, duodenitis or ulcers).

Adverse reactions such as oesophagitis, oesophageal ulcers and oesophageal erosions, in some cases severe and requiring hospitalization, rarely with bleeding or followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. The risk of severe oesophageal adverse experiences appears to be greater in patients who do not comply with the dosing instruction and/or who continue to take oral bisphosphonates after developing symptoms suggestive of oesophageal irritation. Patients should pay particular attention and be able to comply with the dosing instructions.

Clinicians should be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue ibandronic acid and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain, or new or worsening heartburn. While no increased risk was observed in controlled clinical trials there have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications.

Osteonecrosis of the jaw (ONJ)

ONJ has been reported very rarely in the post marketing setting in patients receiving ibandronic acid for oncology indications.

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth.

A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with ibandronic acid in patients with concomitant risk factors.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

- Potency of the medicinal product that inhibit bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapyCancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with ibandronic acid. While on treatment, invasive dental procedures should be

performed only after careful consideration and be avoided in close proximity to ibandronic acid administration.

For management on ONJ, please see the adverse effects table above.

Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique, fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. 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 any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Renal function

Clinical studies have not shown any evidence of deterioration in renal function with long term ibandronic acid therapy. Nevertheless, according to clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with ibandronic acid.

Rare hereditary problems

Ibandronic acid tablets contain lactose and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Patients with known hypersensitivity to other bisphosphonates

Caution is indicated in patients with known hypersensitivity to other bisphosphonates

Further information on bisphosphonate use and safety may be found from guidance produced by the MHRA

Effects on ability to drive and operate machinery: None

Pregnancy:

There are no adequate data from the use of ibandronic acid in pregnant women. Studies in rats have shown reproductive toxicity. The potential risk for humans is unknown. Therefore, ibandronic acid should not be used during pregnancy.

Breast-feeding:

It is not known whether ibandronic acid is excreted in human milk. Studies in lactating rats have demonstrated the presence of low levels of ibandronic acid in the milk following intravenous administration. Ibandronic acid should not be used during lactation.

Fertility:

There are no data on the effects of ibandronic acid from humans. In reproductive studies in rats by the oral route, ibandronic acid decreased fertility. In studies in rats using the intravenous route, ibandronic acid decreased fertility at high daily doses.

Drug Interactions

Metabolic interactions are not considered likely, since ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce hepatic cytochrome P450 system in rats. Ibandronic acid is eliminated by renal excretion only and does not undergo biotransformation.

H_2antagonists or other medicinal products that increase gastric PH

In healthy male volunteers and postmenopausal women, intravenous ranitidine caused an increase in ibandronic acid bioavailability of about 20% (which is within the normal variability of the bioavailability of ibandronic acid), probably as a result of reduced gastric acidity. However, no dosage adjustment is required when ibandronic acid is administered with H_2-antagonists or other drugs that increase gastric pH.

Acetylsalicylic acid and NSAIDs

Since Acetylsalicylic acid. Nonsteroidal Anti-Inflammatory medicinal products (NSAIDs) and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration.

Aminoglycosides

Caution is advised when bisphosphonates are administered with aminoglycosides, since both substances can lower serum calcium levels for prolonged periods. Attention should also be paid to the possible existence of simultaneous hypomagnesaemia.

Please refer to SPC/BNF for full information on interactions with drug name and how to manage these interactions.

Clinical Monitoring

Test	Frequency	Action if out of range
Calcium	6 monthly	Decreased renal calcium excretion may be accompanied by a fall in serum phosphate levels not requiring therapeutic measures. The serum calcium level may fall to hypocalcaemic values – in this case, ensure patient is taking calcium and vitamin D supplementation throughout adjuvant ibandronic acid therapy with the equivalent of 1,000 mg of calcium daily and 800 IU of vitamin D – options include Accrete D3, Evacal D3 or Cacit D3.
Creatinine and creatinine clearance	6 monthly	If creatinine clearance has fallen, dose adjustment of ibandronic acid may be needed. The GP can amend the dose of ibandronic acid as per the patient's renal function tests without needing to confirm with the oncology specialist. Ibandronic acid is not expected to cause renal dysfunction therefore causes of new renal impairment should be investigated.

Any suspected adverse reactions should be reported using the Yellow Card Scheme.

Contact Details

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References

1. Accord-UK Ltd. Ibandronic Acid 50mg Film-coated Tablets - Summary of Product Characteristics. Published December 28, 2018. Accessed November 26, 2021. https://www.medicines.org.uk/emc/product/4642/smp