IBANDRONIC ACID

Class: Bisphosphonate.

Indications: Cancer-induced hypercalcaemia, prevention of skeletal events in patients with breast cancer and bone metastases; †metastatic bone pain.

Pharmacology

Ibandronic acid is a third-generation bisphosphonate. In patients with hypercalcaemia, normocalcaemia is achieved in 1/2–2/3 and 3/4 of patients after single IV doses of 2 and 4 mg, respectively. Increasing the dose to 6mg IV does not increase the response (3/4). Median times to relapse vary from 2–4 weeks depending on the dose. In an open randomised comparison ibandronic acid 4mg IV was as effective as pamidronate 60mg IV, with 3/4 of patients achieving normocalcaemia after the first dose. Ibandronic acid has not been compared to zoledronic acid, which is more effective than pamidronate in hypercalcaemia.4

Ibandronic acid, given either as 50mg PO o.d. or 6mg IV every 3–4 weeks, reduces skeletal events (fractures or need for radiotherapy or surgery) due to bone metastases in breast cancer.5,6 Relative efficacy has not been compared between routes or with other bisphosphonates. The ability of ibandronic acid to prevent the development of bone metastases in women with breast cancer is being explored.7 In randomised, double-blind placebo-controlled trials, ibandronic acid 50mg PO o.d. and 6mg IV every 3–4 weeks improved bone pain and quality of life in patients with breast cancer. The mean reduction in pain ranged from 0.1 to 0.3 on a 5-point pain scale, compared to an increase of 0.2 with placebo.8,9 Open studies have suggested efficacy in patients with painful bone metastases from other types of cancer. In patients with prostate cancer given ibandronic acid 6mg IV every 4 weeks, 1/3 became pain-free and 2/3 had partial improvement after a mean of 3 days (range 1–5 days). Relief was maintained for a mean of 24 weeks (range 16–43 weeks).10 In patients with various cancers (mostly breast cancer), ibandronic acid 4mg IV o.d. for 4 consecutive days reduced bone pain within 7 days. Analgesia was maintained for >6 weeks. Quality of life and functional status were also improved. There was no overall reduction in opioid requirements.11 Ibandronic acid has not been compared to other bisphosphonates for bone pain.

The bio-availability of ibandronic acid is low (<1%). It is reduced further (by up to 90%) by milk, food, antacids and medicines containing iron or calcium and these should be avoided for 30–60min after administration. Despite its poor bio-availability, ibandronic acid 50mg PO o.d. achieves a similar mean plasma concentration, expressed as area under the concentration/time curve, to ibandronic acid 6mg IV once a month.12 However, the actions of bisphosphonates are related to their concentrations in bone, not plasma, and so clinical equivalence cannot be assumed.13 Around half of the dose is rapidly adsorbed onto bone and most of the remainder is bound to plasma proteins. Ibandronic acid is excreted unchanged via the kidneys. The plasma proportion of the drug is rapidly eliminated, mostly within 24h. Thereafter, elimination is much slower as the remainder gradually seeps out of bone.

Ibandronic acid is as well tolerated as pamidronate and there is a low incidence of undesirable effects during long-term follow-up, up to 4 years.3,14,15 Because of concerns about the renal effects of bisphosphonates the renal safety of ibandronic acid has been specifically examined. Although undesirable renal effects are generally uncommon and occur at a similar rate with placebo, increased serum creatinine has been observed in 3% of patients receiving IV ibandronic acid and 1% receiving PO treatment, while renal failure developed in 1% of those on PO treatment.16 In a direct comparison, there were no renal effects among 37 patients receiving ibandronic acid, whereas one of 34 pamidronate-treated patients developed renal failure.3 There are no clinical comparisons of renal safety between ibandronic acid and zoledronic acid. A shorter infusion schedule of 15min is being investigated for ibandronic acid. Nonetheless, the SPC
recommends that patients should be well hydrated, renal function should be monitored during treatment and the dose should be reduced in severe renal impairment.

**Bio-availability** <1% PO.

**Time to peak plasma concentration** <1h.

**Onset of action** normocalcaemia achieved after a median of <4 days;\(^1\,^2\) bone pain relieved after a median of 3 days (range 1–5 days).\(^10\)

**Plasma halflife** 3h; terminal elimination halflife 10–60h.\(^13\)

**Duration of action** hypercalcaemia 2.5 weeks (4mg IV), 4 weeks (6mg IV);\(^2\) bone pain >6 weeks (4mg IV o.d. for 4 days);\(^11\) other IV regimens and PO no data.

**Cautions**

Pre-existing or bisphosphonate-induced hypocalcaemia (correct before starting treatment; calcium and vitamin D supplements should be given if dietary intake is inadequate). Hypovolaemia (correct before treatment and monitor renal function). Severe renal impairment (dose reduction required if creatinine clearance <30ml/min). Concurrent use with aminoglycosides (both can lower serum calcium and magnesium concentrations for prolonged periods).

PO administration: oesophagitis and oropharyngeal, oesophageal and gastric ulceration (discontinue if dysphagia, pain on swallowing, retrosternal pain or heartburn occur). Concurrent use with NSAIDs (both can cause gastro-intestinal irritation and ulceration).

**Undesirable effects**

For full list, see manufacturer’s SPC.

**Very common (>10%):** pyrexia.

**Common (<10%, >1%):** asthenia, flu-like symptoms, headache, hypocalcaemia, bone pain, myalgia. Oral preparations may cause nausea, dyspepsia, or oesophagitis.

**Very rare (<0.01%):** bronchospasm.

**Dose and use**

**Tumour-induced hypercalcaemia**

Patients should be well hydrated, using 0.9% saline if necessary:

- if the corrected serum calcium is >3mmol/L give 4mg
- if the corrected serum calcium is <3mmol/L give 2mg
- for both, the dose is given IV in 500ml 0.9% saline or 5% glucose over 2h.

**Prevention of skeletal events in patients with bone metastases from breast cancer**

- 6mg IV in 500ml 0.9% sodium chloride or 5% glucose over 1h every 3–4 weeks, or
- 50mg PO o.d.

**Metastatic bone pain**

- 6mg IV every 3–4 weeks, or
- 50mg PO o.d.

Ideally, to maximise absorption and to minimise gastro-oesophageal undesirable effects, ibandronic acid tablets should be taken after an overnight fast, with no food for at least a further 30min. The tablets should be swallowed whole in the sitting or standing position, and patients should not lie down for 1h afterwards. They should be taken with a glass of plain tap water (not mineral water because this can contain considerable amounts of calcium).

Dose reduction is recommended in the SPC for patients with severe renal impairment (creatinine clearance <30ml/min) being treated to prevent skeletal events:

- give only 2mg IV over 1h every 3–4 weeks, or
- only 50mg PO once a week.

The SPC gives no recommended dose reductions for patients with bone pain or hypercalcaemia but similar precautions would seem logical.
Ibandronic acid is removed by haemodialysis. Following a single dose of 1mg IV, the serum concentration was successively reduced by approximately 50% at each of 3 sessions. Ibandronic acid was undetectable after the third session.¹⁷

Supply
Bondronat® (Roche 0800 328 1629)

**Tablets** 50mg, 28 days @ 50mg o.d. = £195.00.

**Injection** 2mg/2ml, 6mg/6ml, for dilution and use as an infusion, 2ml amp = £94.86; 6ml vial = £195.00.

---


