Package leaflet: Information for the patient

Bondronat 6 mg concentrate for solution for infusion
ibandronic acid

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor, pharmacist or nurse
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet:

1. What Bondronat is and what it is used for

Bondronat contains the active substance ibandronic acid. This belongs to a group of medicines called bisphosphonates.

Bondronat is used in adults and prescribed to you if you have breast cancer that has spread to your bones (called 'bone metastases')
- It helps to prevent your bones from breaking (fractures)
- It helps to prevent other bone problems that may need surgery or radiotherapy

Bondronat can also be prescribed if you have a raised calcium level in your blood due to a tumour.

Bondronat works by reducing the amount of calcium that is lost from your bones. This helps to stop your bones from getting weaker.

2. What you need to know before you receive Bondronat

Do not receive Bondronat:
- if you are allergic to ibandronic acid or any of the other ingredients of this medicine that are listed in section 6
- if you have, or have ever had low levels of calcium in your blood

Do not receive this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before having Bondronat.

Warnings and precautions
A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported very rarely in the post marketing setting in patients receiving Bondronat for cancer-related conditions. ONJ can also occur after stopping treatment.

It is important to try and prevent ONJ developing as it is a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take.

Before receiving treatment, tell your doctor/nurse (health care professional) if:
- you have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction
- you don't receive routine dental care or have not had a dental check up for a long time
- you are a smoker (as this may increase the risk of dental problems)
- you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders)
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- you have cancer

Your doctor may ask you to undergo a dental examination before starting treatment with Bondronat.

While being treated, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Bondronat.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Talk to your doctor, pharmacist or nurse before receiving Bondronat:
- if you are allergic to any other bisphosphonates
- if you have high or low levels of vitamin D, calcium or any other minerals
- if you have kidney problems
- If you have heart problems and the doctor recommended to limit your daily fluid intake

Cases of serious, sometimes fatal allergic reaction have been reported in patients treated with intravenous ibandronic acid.
If you experience one of the following symptoms, such as shortness of breath/difficulty breathing, tight feeling in throat, swelling of tongue, dizziness, feeling of loss of consciousness, redness or swelling of face, body rash, nausea and vomiting, you should immediately alert your doctor or nurse (see section 4).

Children and adolescents
Bondronat should not be used in children and adolescents below the age of 18 years.

Other medicines and Bondronat
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Bondronat can affect the way some other medicines work. Also, some other medicines can affect the way Bondronat works.

In particular, tell your doctor or pharmacist if you are receiving a type of antibiotic injection called 'aminoglycoside' such as gentamicin. This is because aminoglycosides and Bondronat can both lower the amount of calcium in your blood.

Pregnancy and breast-feeding
Do not receive Bondronat if you are pregnant, planning to get pregnant or if you are breast-feeding. Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
You can drive and use machines as it's expected that Bondronat has no or negligible effect on your ability to drive and use machines. Talk to your doctor first if you want to drive, use machines or tools.

Bondronat contains less than 1 mmol sodium (23 mg) per vial, i.e. 'essentially sodium free'.

3. How to receive Bondronat

Receiving this medicine
- Bondronat is normally given by a doctor or other medical staff who have experience with the treatment of cancer
- It is given as an infusion into your vein

Your doctor may do regular blood tests while you are receiving Bondronat. This is to check that you are being given the right amount of this medicine.

How much to receive
Your doctor will work out how much Bondronat you will be given depending on your illness.
If you have breast cancer that has spread to your bones, then the recommended dose is 1 vial (6 mg) every 3-4 weeks, as an infusion in your vein over at least 15 minutes.

If you have a raised calcium level in your blood due to a tumour, then the recommended dose is a single administration of 2 mg or 4 mg depending on the severity of your illness. The medicine should be administered as an infusion in your vein over two hours. A repeated dose may be considered in case of insufficient response or if your illness reappears.

Your doctor may adjust your dose and duration of intravenous infusion if you have kidney problems.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

Talk to a nurse or a doctor straight away if you notice any of the following serious side effects you may need urgent medical treatment:

Rare (may affect up to 1 in 1,000 people)
- persistent eye pain and inflammation
- new pain, weakness or discomfort in your thigh, hip or groin. You may have early signs of a possible unusual fracture of the thigh bone

Very rare (may affect up to 1 in 10,000 people)
- pain or sore in your mouth or jaw. You may have early signs of severe jaw problems (necrosis (dead bone tissue) in the jaw bone)
- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.
- itching, swelling of your face, lips, tongue and throat, with difficulty breathing. You may be having a serious, potentially life threatening allergic reaction (see section 2)
- severe adverse skin reactions

Not known (frequency cannot be estimated from the available data)
- asthma attack

Other possible side effects

Common (may affect up to 1 in 10 people)

- flu-like symptoms, including fever, shaking and shivering, feeling of discomfort, fatigue, bone pain and aching muscles and joints. These symptoms usually disappear within a couple of hours or days. Talk to a nurse or doctor if any effects become troublesome or last more than a couple of days
- rise in body temperature
- stomach and tummy pain, indigestion, being sick, vomiting or having diarrhoea (loose bowels)
- low calcium or phosphate levels in your blood
- changes in blood test results such as Gamma GT or creatinine
- a heart rhythm problem called 'bundle branch block'
- pain in your bone or muscles
- headache, feeling dizzy or feeling weak
- feeling thirsty, sore throat, changes in taste
- swollen legs or feet
- aching joints, arthritis, or other joint problems
- problems with your parathyroid gland
- bruising
- infections
- a problem with your eyes called 'cataracts'
- skin problems
- tooth problems

Uncommon (may affect less than 1 in 100 people)

- shaking or shivering
- your body temperature getting too low ('hypothermia')
- a condition affecting the blood vessels in your brain called 'cerebrovascular disorder'" (stroke or brain bleeding)
- heart and circulatory problems (including palpitations, heart attack, hypertension (high blood pressure) and varicose veins)
- changes in your blood cells ('anaemia')
- a high level of alkaline phosphatase in your blood
- fluid build up and swelling ('lymphoedema')
- fluid in your lungs
- stomach problems such as 'gastroenteritis' or 'gastritis'
- gallstones
- being unable to pass water (urine), cystitis (bladder inflammation)
- migraine
- pain in your nerves, damaged nerve root
- deafness
- increased sensitivity of sound, taste or touch or changes in smell
- difficulty swallowing
- mouth ulcers, swollen lips ('cheilitis'), oral thrush
- itching or tingling skin around your mouth
- pelvic pain, discharge, itching or pain in the vagina
- a skin growth called a 'benign skin neoplasm'
- memory loss
- sleep problems, feeling anxious, emotional instability, or mood swings
- skin rash
- hair loss
- injury or pain at the injection site
- weight loss
- kidney cyst (fluid-filled sac in the kidney)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

5. How to store Bondronat

- Keep this medicine out of the sight and reach of children
- Do not use this medicine after the expiry date which is stated on the folding box and on the label after EXP. The expiry date refers to the last day of that month
- After dilution the infusion solution is stable for 24 hours at 2-8 °C (in a refrigerator)
- Do not use this medicine if you notice that the solution is not clear or contains particles

6. Content of the pack and other information

What Bondronat contains
- The active substance is ibandronic acid. One vial with 6 ml of a concentrate for solution for infusion contains 6 mg ibandronic acid (as sodium monohydrate)
- The other ingredients are sodium chloride, acetic acid, sodium acetate and water for injections

What Bondronat looks like and contents of the pack
Bondronat is a colourless, clear solution. Bondronat is supplied as packs containing 1, 5 and 10 vials (6 ml type I glass vial with a bromobutyl rubber stopper). Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Atnahs Pharma UK Limited
Sovereign House
Miles Gray Road
Basildon
Essex
SS14 3FR
United Kingdom

Manufacturer
Waymade PLC
Sovereign House,
Miles Gray Road,
Basildon, Essex,
SS14 3FR
United Kingdom

Waymade PLC
Josselin Road
Burnt Mills Industrial Estate
Basildon, SS13 1QF
United Kingdom

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

The following information is intended for healthcare professionals only

Dosage: Prevention of Skeletal Events in Patients with Breast Cancer and Bone Metastases
The recommended dose for prevention of skeletal events in patients with breast cancer and bone metastases is 6 mg intravenously given every 3-4 weeks. The dose should be infused over at least 15 minutes.

Patients with renal impairment
For patients with mild renal impairment (CLcr ≥50 and <80 mL/min) no dosage adjustment is necessary. For patients with moderate renal impairment (CLcr ≥30 and <50 mL/min) or severe renal impairment (CLcr <30 mL/min) being treated for the prevention of skeletal events in patients with breast cancer and metastatic bone disease the following dosing recommendations should be followed:

Creatinine Clearance (ml/min)	Dosage		Infusion Volume [1] and Time [2]
≥50 CLcr<80	6 mg	(6 ml of concentrate for solution for infusion)	100 ml over 15 minutes
≥30 CLcr <50	4 mg	(4 ml of concentrate for solution for infusion)	500 ml over 1 hour
<30	2 mg	(2 ml of concentrate for solution for infusion)	500 ml over 1 hour

[1] 0.9% sodium chloride solution or 5% glucose solution
[2] Administration every 3 to 4 week

A 15 minute infusion time has not been studied in cancer patients with CLCr <50 mL/min.

Dosage: Treatment of Tumour-induced Hypercalcaemia
Bondronat is usually administered in a hospital setting. The dose is determined by the doctor considering the following factors.

Prior to treatment with Bondronat the patient should be adequately rehydrated with 9 mg/ml (0.9%) sodium chloride. Consideration should be given to the severity of the hypercalcaemia as well as the tumour type. In most patients with severe hypercalcaemia (albumin-corrected serum calcium* ≥3 mmol/l or ≥12 mg/dl) 4 mg will be an adequate single dosage. In patients with moderate

hypercalcaemia (albumin-corrected serum calcium <3 mmol/l or <12 mg/dl) 2 mg is an effective dose. The highest dose used in clinical trials was 6 mg but this dose does not add any further benefit in terms of efficacy.

* Note albumin-corrected serum calcium concentrations are calculated as follows:

Albumin-corrected Serum calcium (mmol/l)	=	Serum calcium (mmol/l) - [0.02 x albumin (g/l)] + 0.8
		or
Albumin-corrected Serum calcium (mg/dl)	=	Serum calcium (mg/dl) + 0.8 x [4 - albumin (g/dl)]

To convert the albumin-corrected serum calcium in mmol/l value to mg/dl, multiply by 4.

In most cases a raised serum calcium level can be reduced to the normal range within 7 days. The median time to relapse (re-increase of serum albumin corrected serum calcium above 3 mmol/l) was 18-19 days for the 2 mg and 4 mg doses. The median time to relapse was 26 days with a dose of 6 mg.

Method and route of administration
Bondronat concentrate for solution for infusion should be administered as an intravenous infusion.

For this purpose the contents of the vial are to be used as follows:

- Prevention of Skeletal Events in patients with breast cancer and bone metastases - added to 100 ml isotonic sodium chloride solution or 100 ml 5% dextrose solution and infused over at least 15 minutes. See also dosage section above for patients with renal impairment
- Treatment of tumour-induced hypercalcaemia - added to 500 ml isotonic sodium chloride solution or 500 ml 5% dextrose solution and infused over 2 hours

Note:
In order to avoid potential incompatibilities, Bondronat concentrate for solution for infusion should only be mixed with isotonic sodium chloride solution or with 5% dextrose solution. Calcium containing solutions should not be mixed with Bondronat concentrate for solution for infusion.

Diluted solutions are for single use. Only clear solutions without particles should be used.

It is recommended that the product once diluted be used immediately (see point 5 of this leaflet ‘How to store Bondronat’).

Bondronat concentrate for solution for infusion should be administered as an intravenous infusion. Care must be taken not to administer Bondronat concentrate for solution for infusion via intra-arterial or paravenous administration, as this could lead to tissue damage.

Frequency of administration
For treatment of tumour induced hypercalcaemia, Bondronat concentrate for solution for infusion is generally given as a single infusion.

For the prevention of skeletal events in patients with breast cancer and bone metastases, the Bondronat infusion is repeated at 3-4 week intervals.

Duration of treatment
A limited number of patients (50 patients) have received a second infusion for hypercalcaemia. Repeated treatment may be considered in case of recurrent hypercalcaemia or insufficient efficacy.

For patients with breast cancer and bone metastases, Bondronat infusion should be administered every 3-4 weeks. In clinical trials, therapy has continued for up to 96 weeks.

Overdose
Up to now there is no experience of acute poisoning with Bondronat concentrate for solution for infusion. Since both the kidney and the liver were found to be target organs for toxicity in preclinical studies with high doses, kidney and liver function should be monitored.

Clinically relevant hypocalcaemia (very low serum calcium levels) should be corrected by intravenous administration of calcium gluconate.