Public Assessment Report

Decentralised Procedure

CLASTEON 800MG FILM-COATED TABLETS
(Sodium clodronate)

Procedure No: UK/H/3419/001/DC

UK Licence No: PL 18157/0225

BEACON PHARMACEUTICALS LIMITED
LAY SUMMARY

On 18 August 2011, Ireland, Malta and the UK agreed to grant a Marketing Authorisation to Beacon Pharmaceuticals Limited for the medicinal product Clasteon 800mg film-coated tablets (PL 18157/0225; UK/H/3419/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 05 October 2011.

This is a Prescription-Only Medicine (POM) used to manage bone diseases, particularly those associated with cancer. It also helps to maintain normal levels of calcium in your blood.

Clasteon 800mg film-coated tablets contain the active ingredient sodium clodronate which belongs to a group of medicines called bisphosphonates.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Clasteon 800mg film-coated tablets outweigh the risks and a Marketing Authorisation was granted.
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## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Clasteon 800mg film-coated tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Sodium clodronate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>800mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Beacon Pharmaceuticals Limited</td>
</tr>
<tr>
<td></td>
<td>85 High Street, Tunbridge Wells, Kent TN1 1YG, UK</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member State (CMS)</strong></td>
<td>Ireland and Malta</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/3419/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 198–18 August 2011</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
CLASTEON® 800mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1000mg of disodium clodronate tetrahydrate, equivalent to 800mg of anhydrous sodium clodronate. Each tablet contains 128.24 mg sodium. For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM
Film coated tablets.
White, oval, convex tablet with breakline. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Sodium clodronate is indicated for the management of osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with carcinoma of the breast or multiple myeloma. Sodium clodronate tablets are also indicated for the maintenance of clinically acceptable serum calcium levels in patients with hypercalcaemia of malignancy initially treated with an intravenous bisphosphonate.

4.2 Posology and method of administration
Adequate fluid intake should be maintained during treatment. A Clasteon 800mg tablet may be divided into two to ease swallowing, but the halves have to be taken at the same time of administration. Clasteon tablets should not be crushed or dissolved before intake.

Adults: The recommended daily dose is 2 tablets (1600mg sodium clodronate) taken as a single dose. If clinically necessary, the dose may be increased, but is not recommended to exceed 3200 mg daily.

Intravenous clodronate is recommended for the treatment of hypercalcaemia due to malignancy. However, if oral therapy is used, a high starting dose of 2400 or 3200 mg daily should be used and, depending on the individual response, this can be reduced gradually to 1600 mg daily in order to maintain normocalcaemia.

When higher daily doses are used, the part of the dose exceeding 1600 mg should be taken separately (as a second dose) as recommended below.

The single daily dose and the first dose of two should preferably be taken in the morning on an empty stomach together with a glass of water. The patient should then refrain from eating, drinking (other than plain water), and taking any other oral drugs for one hour.

When twice daily dosing is used, the first dose should be taken as recommended above. The second dose should be taken between meals, more than two hours after and one hour before eating, drinking (other than plain water), or taking any other oral drugs.

Clodronate should in no case be taken with milk, food or drugs containing calcium or other divalent cations because they impair the absorption of clodronate.

Elderly: There are no special dosage recommendations in the elderly. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

Children: Safety and efficacy in children have not been established.

Use in renal impairment: Clodronate is eliminated mainly via the kidneys. Therefore, it should be used with caution in patients with renal failure; daily doses exceeding 1600mg should not be used continuously.

In patients with mild renal failure with creatinine clearance 50 – 80ml/min. no dosage reduction is recommended. In patients with moderate renal failure (creatinine clearance 30-49 ml/min) the daily dose should be reduced to 1200mg sodium clodronate.
In patients with severe renal failure with creatinine clearance 10 – 29ml/min. the daily dose should be reduced to half the adult dose, i.e. 800 mg sodium clodronate. Sodium clodronate is contraindicated in patients with creatinine clearance below 10 ml/min.

### Dosage for Patients with Renal Failure

<table>
<thead>
<tr>
<th>Degree of renal failure</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>50-80</td>
<td>1600mg daily (no dose reduction recommended)</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-49</td>
<td>1200mg daily</td>
</tr>
<tr>
<td>Severe</td>
<td>10-29</td>
<td>800mg daily</td>
</tr>
</tbody>
</table>

The oral bioavailability of bisphosphonates is poor. Bioequivalence studies have shown appreciable differences in bioavailability between different oral formulations of sodium clodronate, as well as marked inter and intra patient variability. Dose adjustment may be required if the formulation is changed.

### 4.3 Contraindications

Sodium clodronate tablets are contraindicated in patients with severe renal failure where creatinine clearance less than 10 ml/min, hypersensitivity to the active substance or to any of the excipients and in patients receiving concomitant treatment with other bisphosphonates.

### 4.4 Special warnings and precautions for use

Adequate fluid intake should be maintained during treatment. Sodium clodronate should be administered with care to patients with renal insufficiency. It is recommended that appropriate monitoring of hydration status and renal function with serum creatinine measurement be carried out during treatment. Serum calcium should be monitored periodically. Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. This medicinal product contains 128.24 mg sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

### 4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of other bisphosphonates is contraindicated. As aminoglycosides can cause hypocalcaemia, concomitant clodronate should be administered with caution.

Patients receiving NSAID's in addition to sodium clodronate have developed renal dysfunction. However, a synergistic action has not been established.

Concomitant use of estramustine phosphate with clodronate has been reported to increase the serum concentration of estramustine phosphate by 80% at the maximum.

Sodium clodronate forms complexes with divalent ions, and therefore simultaneous administration with food, antacids, and mineral supplements may impair absorption.
4.6 **Fertility, Pregnancy and lactation**
There are limited amount of data from the use of clodronate in pregnant women. Sodium clodronate is not recommended during pregnancy and in women of childbearing potential not using effective contraception. Although in animals clodronate passes through the placental barrier, it is not known if it passes into the foetus in humans. Furthermore, it is not known if clodronate can cause foetal damage or affect reproduction in humans. Studies in animals have shown reproductive toxicity (see section 5.3).

It is unknown whether clodronate is excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with sodium clodronate.

4.7 **Effects on ability to drive and use machines**
No effects.

4.8 **Undesirable effects**
The most common reported drug reaction is diarrhoea which is usually mild and occurs more commonly with higher doses.

These adverse reactions may occur when using sodium clodronate:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Rare</th>
<th>Frequency unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Asymptomatic hypocalcaemia.</td>
<td>Symptomatic hypocalcaemia. Increased levels of serum parathyroid hormone associated with decreased serum calcium levels. Increased levels of serum alkaline phosphatase.*</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Diarrhoea**</td>
<td>Nausea**</td>
<td>Vomiting**</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>Levels of transaminases increased – usually within normal range.</td>
<td>Levels of transaminases increased to more than twice the normal range without associated abnormal hepatic function.</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Hypersensitivity reaction manifesting as skin reaction e.g. pruritus, urticaria, exfoliative dermatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Bronchospasm in patients with and without a previous history of asthma.</td>
<td>Impairment of respiratory function in patients with aspirin-sensitive asthma. Hypersensitivity reactions manifesting as respiratory disorder.</td>
<td></td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td>Impairment of renal function (elevation of serum creatinine and proteinuria), severe renal damage. Single cases of renal failure, in rare cases with fatal outcome, especially with concomitant use of</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>NSAIDs, most often diclofenac.</td>
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<td></td>
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<tr>
<td></td>
<td>Isolated cases of osteonecrosis of the jaw, primarily in patients previously treated with amino-bisphosphonates such as zoledronate and pamidronate (see section 4.4). Severe bone, joint and/or muscle pain has been reported in patients taking sodium clodronate. However, such reports have been infrequent and in randomised placebo controlled studies no differences are apparent between placebo and sodium clodronate treated patients. The onset of symptoms varied from days to several months after starting sodium clodronate.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* in patients with metastatic disease, may also be due to hepatic and bone disease.

** usually mild – use of the divided dose regimen rather than a single daily dose may improve gastrointestinal tolerance.

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

4.9 Overdose

**Symptoms:**
Increases in serum creatinine and renal dysfunction have been reported with high intravenous doses of clodronate. It is theoretically possible that hypocalcaemia may develop up to 2 or 3 days following the overdose.

**Treatment:**
Treatment of overdose should be symptomatic. Adequate hydration should be ensured, and renal function and serum calcium should be monitored. Serum calcium should be monitored and oral or parenteral calcium supplementation may be needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Bisphosphonates
ATC code: M05B A02

Clodronate is a bisphosphonate, (formerly diphosphonates), a group of analogues of pyrophosphate, which have been shown, in vitro, to inhibit the formation and dissolution of calcium phosphate (hydroxyapatite). In vivo, they have been shown to inhibit bone resorption to a greater or lesser extent, depending on the compound, and clodronate is one of the most effective in this respect.

However, the most important mechanism of action of clodronate is its inhibitory effect on osteoclastic bone resorption. Clodronate inhibits bone resorption induced in several ways. In growing rats, this inhibition of bone resorption at high doses of clodronate causes broadening of long bone metaphyses.

In ovariectomized rats, bone resorption is inhibited at doses as low as 3 mg/kg administered subcutaneously once a week. At pharmacological doses clodronate prevents reduction of bone strength.
The pharmacological efficacy of clodronate has been demonstrated in different types of preclinical experimental models of osteoporosis, including estrogen deficiency. Clodronate has been shown to inhibit dose-dependently bone resorption, without deleterious effects on mineralization or on other bone quality aspects. Bone resorption in experimental renal osteodystrophy is also inhibited by clodronate.

The ability of clodronate to inhibit bone resorption in humans has been established in histological, kinetic and biochemical studies. However, the exact mechanisms of bone resorption inhibition are partly unknown. Clodronate suppresses the activity of osteoclasts, reducing the serum calcium concentration and urinary excretion of calcium and hydroxyproline. Clodronate prevents bone loss associated with breast cancer in the hip and lumbar spine in pre- and postmenopausal women. When clodronate is used alone at doses inhibiting bone resorption, no effects on normal bone mineralization in humans have been observed. A decrease in fracture risk has been observed in patients with breast cancer and multiple myeloma.

5.2 Pharmacokinetic properties
Absorption
As with other bisphosphonates, the gastrointestinal absorption of clodronate is low, about 2%. The absorption of clodronate is rapid, the peak serum concentration after a single oral dose is reached within 30 minutes. Due to the strong affinity of clodronate for calcium and other divalent cations, the absorption is negligible when clodronate is taken with meals or drugs containing divalent cations. In a study, where clodronate administration 2 h before breakfast was used as the reference treatment, a dose-breakfast interval of 1 h or 0.5 h decreased the bioavailability of clodronate, but the difference was not statistically significant (relative bioavailability 91% and 69%, respectively). In addition, there is large inter- and intraindividual variation in the gastrointestinal absorption of clodronate. Despite the large intraindividual variation in the absorption of clodronate, the exposure to clodronate remains constant during long-term treatment.

Distribution and elimination
The plasma protein binding of clodronate is low, and the distribution volume is 20-50l. The elimination of clodronate from serum is characterized by two clearly distinguished phases: the distribution phase with a half-life of about 2 hours, and an elimination phase which is very slow because clodronate is strongly bound to bone. Clodronate is mainly eliminated via the kidneys. About 80% of the absorbed clodronate appears in urine during a follow-up of a few days he substance which is bound to bone (about 20% of the absorbed amount) is excreted more slowly, and the renal clearance is about 75% of the plasma clearance.

Clodronate is removed by haemodialysis. When 300 mg was given by slow infusion 2 h before haemodialysis, 35% of the clodronate dose was collected in the 4 hour dialysate.

Characteristics in patients
Because clodronate affects bone there is no clear relationship between plasma or blood concentrations of clodronate and the therapeutic activity or with adverse drug reactions. Apart from renal insufficiency, which decreases the renal clearance of clodronate, the pharmacokinetic profile is not affected by any known factor related to age, drug metabolism or other pathological conditions.

5.3 Preclinical safety data
Systemic tolerance:
Repeated dose oral and intravenous toxicity studies in rats and mini-pigs up to 6 to 12 months duration respectively have been performed. At oral daily doses up to 480 mg/kg in rats and 800 mg/kg in mini-pigs no test substance related mortality was noted. In these studies, the effect of clodronate was observed in the following organs (the observed changes within brackets): bone (sclerosis related to the pharmacological effects of clodronate), gastrointestinal tract (irritation), blood (lymphopenia, effects on hemostasis), kidneys (dilated tubules, proteinuria), and liver (elevation of serum transaminases).

Reproduction toxicity:
In reproductive toxicity studies in the rat, clodronate at exposures at or below clinical exposure levels caused maternal mortality around the time of parturition and is believed to be as a result of hypocalcaemia. In teratology studies in rats and rabbits at oral daily dosages of 200 mg/kg and 300mg/kg respectively (0.5 to 2 times the maximum clinical dose based on body surface area, mg/m^2), no adverse or teratogenic effects were observed in the offspring. At higher doses associated with maternal toxicity, there was reduced litter size in the rabbit and a reduction in foetal body weight, reduced ossification and renal pelvis dilation in the rat.
In fertility studies in the rat, clodronate 600 mg/kg/day in males was associated with reduced body weight, lesions in the testes and epididymides and reduced mating performance. After one month of subcutaneous administration of clodronate to newborn rats, skeletal changes resembling osteopetrosis were found, which are related to the pharmacological effects of clodronate.

Carcinogenicity:
Clodronate has not shown genotoxic potential. No carcinogenic effects have been observed in long term studies with rats and mice.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Starch pregelatinized, microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate (type A) and magnesium stearate. The tablet coating contains: hypromellose, titanium dioxide (E171) and macrogol 400

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
PVC/PVDC/aluminium blister packs: 4 years.

6.4 Special precautions for storage
No special precautions for storage.

6.5 Nature and contents of container
PVC/PVDC/aluminium blister packs containing 10, 30 or 60 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special instructions.

7 MARKETING AUTHORISATION HOLDER
Beacon Pharmaceuticals Limited
85 High Street, Tunbridge Wells, Kent TN1 1YG, UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 18157/0225

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/10/2011

10 DATE OF REVISION OF THE TEXT
05/10/2011
Module 3

Package leaflet: Information for the patient/user

CLAUSTEON 800MG FILM-COATED TABLETS (Sodium clodronate)

Please read this leaflet carefully before taking Clasteon tablets. Keep the leaflet in case you need to refer to it again. If you want to know more about Clasteon tablets or have any questions, you should ask your doctor or pharmacist.

What is this leaflet?
1. What Clasteon tablets are used for
2. Before taking Clasteon tablets
3. How to take Clasteon tablets
4. Possible side effects
5. Storing Clasteon tablets
6. Further information

1. WHAT CLASTEON TABLETS ARE USED FOR

Clasteon tablets contain sodium clodronate, which is one of a group of medicines known as bisphosphonates. These medicines help prevent loss of calcium from bones.

Clasteon tablets are used to manage bone diseases, particularly those associated with cancer. They also help to maintain normal levels of calcium in your blood.

2. BEFORE TAKING CLASTEON TABLETS

You must NOT take Clasteon tablets and should talk to your doctor if:
- you are allergic to sodium clodronate, similar medicines or any of the ingredients (listed in section 6)
- you have very poor kidney function
- you are pregnant or breast feeding
- you are already taking a similar medicine (containing bisphosphonates).

Tell your doctor if:
- you have ever had/ have pain, numbness or swelling of your jaw or a heavy jaw feeling or loosening of a tooth
- you are having dental treatment or will undergo dental surgery, tell your dentist that you are being treated with a bisphosphonate (Sodium clodronate). Certain types of dental treatment are not recommended while taking bisphosphonates
- you have problems with your kidneys.

Taking/using other medicines
Tell your doctor or pharmacist if you are taking or have recently taken any other medicine including those obtained without a prescription.

This is particularly important if you are taking any of the following:
- antibiotics
- non-steroidal anti-inflammatory medicines such as ibuprofen or diclofenac
- antacid indigestion tablets
- mineral supplements

- estramustine, used to treat prostate cancer.
- Do not take any other medicines by mouth for 2 hours before and 1 hour after each dose of Clasteon Tablets.

Food and drink with Clasteon Tablets
It is important that you take your tablets on an empty stomach (otherwise your body will not absorb the drug properly). Except for plain water, do not eat or drink for 2 hours before and 1 hour after each dose. It is particularly important to avoid drinking milk in this period. You can drink water whenever you like.

Pregnancy and breastfeeding
Clasteon Tablets are not normally given to people during pregnancy. If you think you might be pregnant or if you are planning a family, tell your doctor before taking Clasteon Tablets.

Do not breastfeed while you are taking Clasteon Tablets.

Driving and using machines
Clasteon Tablets have no known effect on your ability to drive or use machines.

Important information about some of the ingredients of this medicine
This medicinal product contains 128.24 mg sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO TAKE CLASTEON TABLETS

Always take the tablets exactly as your doctor tells you to.

Clasteon tablets are for use in adults only.

You need to take plenty of fluids (such as water) before, during and after your treatment.

The daily dosage varies. In most cases the dose is between 1600 mg (2 tablets) and 3200 mg (4 tablets) per day. If you have problems with your kidneys then the dose may be reduced.

- Swallow the tablets with plain water. The tablets may be divided into two halves to help with swallowing, but the two halves must not be taken at the same time
- Do not crush or dissolve the tablets and never take them with milk because this reduces the amount of drug that your body can absorb
- Take the tablets at least 2 hours before or 1 hour after food (and avoid milk during this period)
- Take the tablets even if you are not eating at present.

If you have been prescribed a single daily dose of Clasteon Tablets, it should be taken (preferably in the morning) on an empty stomach with a glass of plain water. After using Clasteon Tablets, you should not eat, drink (other than plain water) or take any other medicines by mouth for 1 hour.

If you have been prescribed a twice daily dose, the first dose should be taken as recommended above. The second dose should be taken between meals, more than 2 hours after and 1 hour before eating, drinking (other than plain water), or taking any other medicines by mouth.
If you forget a dose take it as soon as possible. However, if it is nearly time for your next dose, skip the missed dose and carry on as before. Do not take a double dose.

If you take too many Clasteon tablets or someone else accidentally takes your medicine, get medical help immediately and drink plenty of water. If possible, take your tablets with you to show the doctor. Your doctor may want to check the amount of calcium in your blood and how well your kidneys are working.

Symptoms of an overdose may be a feeling of sickness, or being sick (nausea or vomiting). Your doctor has prescribed this medicine for you. Never give it to others as it may harm them, even if their symptoms are the same as yours.

4. POSSIBLE SIDE EFFECTS

As with all medicines Clasteon tablets may cause side effects in some patients.

Stop taking the tablets and contact your doctor if any of the following occur:
- wheezing or difficulty in breathing
- swelling of face, tongue or throat
- itching, rash.

These may be symptoms of an allergic (hypersensitivity) reaction.

If you experience any of the following serious side effects, seek immediate medical attention:
- numbness and tingling sensations around the mouth and/or in the fingers and toes, muscle cramps or spasms (in the back, hands and/or feet) or fits
- kidney problems which can be experienced as feeling generally unwell, a reduced appetite and you may observe foamy urine
- severe kidney damage which may include symptoms such as weakness or tiredness, change in frequency of urination and swelling of the face, arms, legs and abdomen. These problems are more common when taking some types of anti-inflammatory drug (most often diclofenac) at the same time as Clasteon Tablets
- pain, swelling or numbness of the jaw, a "heavy jaw feeling" or loosening of a tooth, especially if you have been treated in the past with bisphosphonates such as zoledronic and pamidronate
- severe bone, joint and/or muscle pain that can start days to several months after starting treatment with Clasteon Tablets

Common side effects (occur in less than 1 in 10 patients):
- low calcium levels in the blood without any symptoms (asymptomatic hypocalcaemia) or small increases in the levels of liver enzymes, which can be detected by blood tests
- being sick, feeling sick (nausea) or diarrhoea. If this happens it may help if you take half the number of tablets in the morning and the rest in the evening.

Rare side effects (occur in less than 1 in 1,000 patients)
- skin reactions
- difficulty breathing
- low calcium levels in the blood with symptoms (symptomatic hypocalcaemia) or small increases in levels of liver enzymes or some hormones

Other side effects (frequency unknown)
- Breathing problems – aspirin sensitive asthma or allergic reactions
- Kidney problems which may include severe kidney damage and has been fatal, this is more common in patients also taking diclofenac
- Dead tissue in the jaw bone (osteonecrosis) seen mainly in patients treated in the past with zoledronic or pamidronate
- Severe bone, joint and/or muscle pain

If you have side effects which do not improve, or any other effects which concern you please tell your doctor or pharmacist.

Your doctor may test your blood from time to time, to check that Clasteon tablets are working correctly.

5. STORING CLASTEON TABLETS

Keep this medicine out of the reach and sight of children.

Do not use Clasteon after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What is in this medicine:
Each tablet contains 800mg of the active ingredient sodium clodronate (as the tetrahydrate).

The other ingredients are starch pregelatinised, microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate (type A) and magnesium stearate. The tablet coating contains: hypromellose, titanium dioxide (E171) and macrogol 400.

What this medicine looks like and contents of the pack:
Clasteon tablets are white oval convex film-coated tablets with a breakline, the breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses. Available in packs of 10, 30 or 60 tablets. Not all pack sizes may be marketed.

The product is called Clasteon 800mg film-coated Tablets in the UK, Ireland and Malta.

Marketing authorisation holder: Beacon Pharmaceuticals Ltd. Tunbridge Wells, Kent TN1 1YG, UK.

Manufacturer: Abiogen Pharma S.p.A., via Meucci 36, Ospeleta - I-56014 Pisa - Italy.

Date of approval: 09/2011

Beacon Pharmaceuticals Ltd,
85 High Street, Tunbridge Wells TN1 1YG, UK.
Module 4
Labelling

Carton:

Braille:
CLASTEON #800MG tablets
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Clasteon 800mg film-coated tablets (PL 18157/0225; UK/H/3419/001/DC) could be approved. This application was submitted by the decentralised procedure, with the UK as Reference Member State (RMS) and Ireland and Malta as Concerned Member States (CMS).

This product is a prescription-only medicine indicated for the management of osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with carcinoma of the breast or multiple myeloma. Clasteon 800mg film-coated tablets are also indicated for the maintenance of clinically acceptable serum calcium levels in patients with hypercalcaemia of malignancy initially treated with an intravenous bisphosphonate.

This application was submitted according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Bonefos 800mg Tablets, which was first authorised to Boehringer Ingleheim Ltd on 03 February 1995 and underwent changes of ownership to Schering Healthcare Ltd (PL 00053/056) and subsequently to the current Marketing Authorisation Holder Bayer plc (PL 0010/0522) on 04 June 2008.

Clasteon 800mg film-coated tablets contain the active ingredient sodium clodronate which belongs to a group of medicines called bisphosphonates which show physicochemical effects very similar to those of pyrophosphate. They bind to hydroxyapatite and inhibit the formation, delay the aggregation and slow down the dissolution of calcium phosphate crystals. Like pyrophosphates, bisphosphonates bind to the surface of crystals and then act as inhibitors of both crystal growth and dissolution. Because of its strong affinity for calcium phosphate, clodronate acts almost solely on calcified tissues, especially bone. Clodronate alters the activities of osteoclasts and osteoblasts and as a consequence the balance of bone resorption and bone formation, resulting in reduction of bone turnover. Clodronate accumulates in bone tissue because it strongly binds to hydroxyapatite crystals. It does not appear to be metabolised and the majority of the absorbed drug is excreted unchanged by the kidneys in the urine.

No new non-clinical studies were conducted, which is acceptable given that the product is intended to be a generic medicinal product of an originator product that has been licensed for over 10 years.

One bioequivalence study (single dose) was submitted to support this application, comparing the test product Clasteon 800mg film-coated tablets (Beacon Pharmaceuticals Limited) with the reference product Bonefos 800 mg tablets (Schering Healthcare Ltd, UK).

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was for a product that is intended to be a generic medicinal product of an originator product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 198) on 18 August 2011. After a subsequent national phase, the licence was granted in the UK on 05 October 2011.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Clasteon 800mg film-coated tablets |
| Name(s) of the active substance(s) (INN)          | Sodium clodronate                  |
| Pharmacotherapeutic classification (ATC code)    | Bisphosphonates (M05B A02)         |
| Pharmaceutical form and strength(s)             | 800mg film-coated tablets          |
| Reference numbers for the Mutual Recognition Procedure | UK/H/3419/001/DC                  |
| Reference Member State                          | United Kingdom                     |
| Member States concerned                         | Ireland and Malta                  |
| Marketing Authorisation Number(s)               | PL 18157/0225                      |
| Name and address of the authorisation holder    | Beacon Pharmaceuticals Limited      |
|                                                | 85 High Street, Tunbridge Wells, Kent |
|                                                | TN1 1YG, UK                        |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Clodronate disodium tetrahydride
Chemical name: (dichloromethylene) biphosphonate acid disodium salt tetrahydrate.
Structure:

Clodronate disodium tetrahydride is a white crystalline powder

Clodronate disodium tetrahydride is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

P. Medicinal Product
Other Ingredients

Other ingredients consist of the pharmaceutical excipients starch pregelatinised, microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate (type A), magnesium stearate, hypromellose, titanium dioxide (E171) and macrogol 400.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.
None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The objective of the development programme was to formulate a tablet containing 800mg sodium clodronate, which could be considered a generic medicinal product of Bonefos 800mg Tablet (Bayer plc, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**
The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**
The finished product is packaged in polyvinylchloride/polyvinylidene chloride/aluminium blister strips in pack sizes of 10, 30 or 60 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has submitted the mock-ups for all pack sizes to the relevant regulatory authorities for approval prior to marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 4 years with no special storage conditions.
Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA form is satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of sodium clodronate are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

Suitable justification has been provided for non-submission of an environmental risk assessment. As this product is intended for generic substitution with other products already on the market, it is not considered to increase the environmental risk. Thus, the applicant’s justification is accepted.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, single-dose, two sequence, four period replicate, cross-over study to compare the pharmacokinetics of the test product Clasteon 800mg film-coated tablets versus the reference product Bonefos 800mg Tablets (Schering Healthcare Ltd, UK) in healthy adult volunteers under fasted conditions.
All volunteers received a single oral dose of either the test or reference product as a 1 x 800 mg tablet administered after an overnight fast. The study design included four consecutive periods, during which each volunteer received both formulations (test and reference) twice in four different study periods. Blood samples and urine samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours post dose. The washout period between two consecutive treatments was at least 7 days.

In previous studies, the bioequivalence of clodronic acid has generally been based upon the surrogate end-point of urinary excretion due to the lack of appropriate methods for determination of clodronic acid in plasma/serum. Recently, new methods have been developed that allow the detection of clodronic acid in plasma with a lower quantification limit (LQL) of 3 ng/mL. It was therefore appropriate to base bioequivalence upon plasma data. In consideration of this relatively new method, urine was also collected and stored. If it had not been possible to validate the new plasma method, urinary samples would have been analysed instead.

The pharmacokinetic results for clodronic acid for the test product versus the reference product are presented below [non-transformed values; arithmetic mean, ± standard deviation (SD)]:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} \text{ ng/ml/h}</th>
<th>AUC_{0-\infty} \text{ ng/ml/h}</th>
<th>C_{\text{max}} \text{ ng/ml}</th>
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<tr>
<td>Test (mean)</td>
<td>2586.5 ±2149.8</td>
<td>2801.8 ±2238.6</td>
<td>1015.2 ±1000.2</td>
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<tr>
<td>Standard deviation (SD)</td>
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<tr>
<td>Reference (mean)</td>
<td>2548.8 ±1793.5</td>
<td>2759.1 ±1883.8</td>
<td>1022.4 ±876.7</td>
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<tr>
<td>Standard deviation (SD)</td>
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<td>*Ratio (90% CI)</td>
<td>93.64 (82.13-106.76%)</td>
<td>94.46 (83.32-107.08%)</td>
<td>91.67 (76.30-110.13%)</td>
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\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to t hours  
\( \text{C}_{\text{max}} \) maximum plasma concentration  
\( \text{T}_{\text{max}} \) time for maximum concentration  
*In-transformed values

Due to the high inter-subject variability of \( \text{C}_{\text{max}} \), the enlarged range of 75.00 – 133.00 % was considered for testing bioequivalence. Within subject \( \text{C}_{\text{max}} \) variability for the reference product was 116 %. Statistical analysis results showed that the 90 % CI for \( \text{C}_{\text{max}} \) fell within the widened limits specified above. In addition, the 90 % CI for AUC_{0-t} and AUC_{0-\infty} fell within the limits of 80.00 to 125.00 %. Also for the AUC values, inter-subject variability was pronounced with CV % for AUC_{0-t} and AUC_{0-\infty} of 83.1 % and 79.9 % for test and of 70.4 % and 68.3 % for reference. The applicant has adequately justified the widening of the confidence interval \( \text{C}_{\text{max}} \) in line with Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 rev 1/Corr). The data support the claim that the test product is bioequivalent to the reference product.

**Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for this application.

**Efficacy**
No new efficacy data were submitted and none were required for this application.

**Safety**
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were highlighted by the bioequivalence data.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of this product from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Clasteon 800mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for an application of this type.

Bioequivalence has been demonstrated between the applicant’s Clasteon 800mg film-coated tablets and the reference product Bonefos 800mg Tablets (Schering Healthcare Ltd, UK).

SAFETY
The safety profile of sodium clodronate is well-known. No new unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate, in line with current guidelines.
BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The data support the claim that this product is a generic medicinal product of the reference product Bonefos 800mg Tablets (Schering Healthcare Ltd, UK). Extensive clinical experience with sodium clodronate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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