

**CLASTEON 400MG CAPSULES
PL 18157/0028**

UKPAR

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LAY SUMMARY

The MHRA granted Beacon Pharmaceuticals Ltd a Marketing Authorisation (licence) for the medicinal product CLASTEON 400mg Capsules (PL 18157/0028). This Marketing Authorisation was initially granted to ABIOTEN PHARMA SpA. A change of ownership was granted and the product's name was changed from CLASTEON 400mg capsules, hard to CLASTEON 400mg Capsules. This prescription only medicine (POM) is used to prevent the loss of calcium in bones to the bloodstream.

CLASTEON 400mg Capsules contain the active ingredient sodium clodronate which is a bisphosphonate.

This application is essentially a duplicate of a previously granted application for Loron capsules (Roche Products Limited) and, as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking CLASTEON 400mg Capsules outweigh the risks, hence a Marketing Authorisation has been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted a Marketing Authorisation for the medicinal product CLASTEON 400mg Capsules (PL 18157/0028) to Beacon Pharmaceuticals Ltd on 28 November 2007. This product is a prescription only medicine. The product was initially called CLASTEON 400mg capsules, hard (PL 14326/001) and was licensed to ABIOGEN PHARMA SpA on 08 February 2007. A change of ownership was granted on 15 May 2007 and the product's name was changed on 28 November 2007.

The application was submitted as a complex abridged application according to article 10c of Directive 2001/83/EC as amended, referring to Loron capsules (Roche Products Limited), approved on 01 July 1999.

No new preclinical or clinical data was submitted nor was it necessary for this application, as the data are identical to those of the previously granted reference product. Since the reference product was granted prior to the introduction of current legislation, a Public Assessment Report (PAR) was not generated for it.

The product contains the active ingredient sodium clodronate and 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. CLASTEON 400mg Capsules are also indicated for the maintenance of clinically acceptable serum calcium levels in patients with hypercalcaemia of malignancy initially treated with an intravenous infusion of sodium clodronate.

Sodium clodronate is a bisphosphonate. It suppresses osteoclast mediated bone resorption as judged by bone histology and decreases in serum calcium, urine calcium and urinary excretion of hydroxyproline, without adversely affecting mineralisation.

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The product is formulated as a hard capsule containing the active pharmaceutical ingredient sodium clodronate, as the tetrahydrate, at a strength of 400mg. The excipients present are maize starch, talc, magnesium stearate and sodium starch glycolate. In addition, titanium dioxide, indigotin and gelatin are present in the capsule shell.

The capsules are presented in aluminium-foil sealed PVC/PVdC blisters, in packs of 30, 60 and 120 capsules.

DRUG SUBSTANCE

Sodium clodronate

Although this is an informed consent application, the proposed drug substance manufacturing site is different from that of the reference product.

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

An appropriate specification based on the reference product specification is provided for sodium clodronate.

Analytical methods have been validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided for three batches and comply with the proposed specification.

Sodium clodronate is stored in appropriate packaging.

Stability data have been generated supporting a retest period of 3 years when stored in the proposed packaging.

DRUG PRODUCT

Other ingredients

All excipients used in the manufacture of the capsules are routinely tested for compliance with current relevant international standards.

Satisfactory certificates of analysis have been provided for all excipients.

Gelatine contains material of animal or human origin. A Transmissible Spongiform Encephalopathies (TSE) Certificate has been provided for gelatine confirming that the risk of transmitting TSEs is sufficiently low.

Manufacture

Although this is an informed consent application, the proposed manufacturing site is different from that of the reference product.

A full description and a detailed flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out and the results are satisfactory

Finished product specification

The proposed finished product specification is in line with the reference product and is acceptable. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification. Certificates of analysis have been provided for all standards used.

Container Closure System

Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability data support the proposed shelf-life of 3 years with no special storage conditions.

Bioequivalence/bioavailability

No bioequivalence study is required in support of this application.

SPC, PIL and Labels

The SPC, PIL and labels are pharmaceutically acceptable.

The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 01 July 2008.

CONCLUSION

It is recommended that a Marketing Authorisation should be granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

As this is an informed consent application, no new clinical data have been supplied and none are required.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of CLASTEON 400mg Capsules 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.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

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

The SPC, PIL and labelling are satisfactory and consistent with that for the reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product has been shown to be interchangeable with the reference product. The risk benefit is therefore considered to be positive.

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the Marketing Authorisation application on 03 June 2004.
2	Following standard checks and communication with the applicant, the MHRA considered the application valid on 01 July 2004.
3	Following assessment of the application, the MHRA requested further information on 08 March 2005, 28 February 2006 and 30 June 2006.
4	The applicant responded to the MHRA's requests, providing further information on 09 May 2005, 10 April 2006 and 02 August 2006.
7	The application was determined on 08 February 2007.

CLASTEON 400MG CAPSULES
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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome
30 Mar 2007	CoA	To change the MAH from Abiogen Pharma SpA to Beacon Pharmaceuticals Ltd	Granted 15 May 2007
02 Oct 2007	Type 1B Variation	To change the product name from CLASTEON 400mg Capsules, hard to CLASTEON 400mg Capsules and to change the name of the active from Clodronic acid, disodium salt to Sodium clodronate.	Granted 28 Nov 2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

CLASTEON® 400mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Clasteon capsule contains 400mg sodium clodronate (as the tetrahydrate). For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Hard capsules for oral administration.

Clasteon Capsules are oblong, white and blue, marked "CLASTEON®".

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clasteon 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. Clasteon capsules are also indicated for the maintenance of clinically acceptable serum calcium levels in patients with hypercalcaemia of malignancy initially treated with an intravenous infusion of sodium clodronate

4.2 Posology and method of administration

Adults; The recommended dose is 4 capsules (1600mg sodium clodronate) daily. If necessary, the dosage may be increased but should not exceed a maximum of 8 capsules (3200mg sodium clodronate) daily.

The capsules may be taken as a single dose or in two equally divided doses if necessary to improve gastrointestinal tolerance. Clasteon capsules should be swallowed with a little fluid, but not milk, at least one hour before or one hour after food.

Elderly; No special dosage recommendations.

Children; Safety and efficacy in children has not been established.

Use in renal impairment; In patients with renal insufficiency with creatinine clearance between 10 and 30ml/min, the daily dose should be reduced to one half the recommended adult dose. Serum creatinine should be monitored during therapy. Sodium clodronate is contra-indicated in patients with creatinine clearance below 10ml/min.

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

Hypersensitivity to sodium clodronate. Acute, severe inflammatory conditions of the gastrointestinal tract. Pregnancy and lactation. Renal failure with creatinine clearance below 10ml/min, except for short term use in the presence of purely functional renal insufficiency caused by elevated serum calcium levels. Concomitant use of other bisphosphonates.

4.4 Special warnings and precautions for use

No information is available on the potential carcinogenicity of sodium clodronate, but patients have been treated in clinical trials for up to 2 years. The duration of the treatment is therefore at the discretion of the physician, according to the status of the underlying malignancy.

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.

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

No other bisphosphonate drugs should be given with Clasteon capsules.

The calcium-lowering action of sodium clodronate can be potentiated by the administration of aminoglycosides either concomitantly or one to several weeks apart. Severe hypocalcaemia has been observed in some cases. Hypomagnesaemia may also occur simultaneously. Patients receiving NSAID's in addition to sodium clodronate have developed renal dysfunction. However, a synergistic action has not been established. There is no evidence from clinical experience that sodium clodronate interacts with other medication, such as steroids, diuretics, calcitonin, non NSAID analgesics, or chemotherapeutic agents. Calcium rich foods, mineral supplements and antacids may impair absorption.

4.6 Pregnancy and lactation

There are insufficient data either from animal studies or from experience in humans of the effects of sodium clodronate on the embryo and foetus. No studies have been conducted on excretion in breast milk. Consequently, sodium clodronate is contraindicated in pregnancy and lactation.

4.7 Effects on ability to drive and use machines

No effects.

4.8 Undesirable effects

Patients may experience a mild gastrointestinal upset, usually in the form of nausea or mild diarrhoea. The symptoms may respond to the use of a twice daily dosage regime rather than a single dose. It is not normally required to withdraw therapy or to provide medication to control these effects. Asymptomatic hypocalcaemia has been noted rarely. A reversible elevation of serum parathyroid hormone may occur. In a small proportion of patients, a mild, reversible increase in serum lactate dehydrogenase and a modest transient leucopenia have been reported although these may have been associated with concurrent chemotherapy. Renal dysfunction, including renal failure has been reported. Hypersensitivity reactions have been mainly confined to the skin: pruritus, urticaria and rarely exfoliative dermatitis. However, bronchospasm has been precipitated in patients with or without a previous history of asthma.

4.9 Overdose

Symptoms and signs: There is no experience of acute overdosage in humans. The development of hypocalcaemia is possible for up to 2 or 3 days following the overdosage.

Treatment: Serum calcium should be monitored and oral or parenteral calcium supplementation may be required. Acute overdosage may be associated with gastrointestinal symptoms such as nausea and vomiting. Treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Sodium clodronate is a bisphosphonate which has a high affinity to bone. It is mainly the portion of the dose adsorbed to bone which is pharmacologically active. The pharmacological effect of sodium clodronate is to suppress osteoclast mediated bone resorption as judged by bone histology and decreases in serum calcium, urine calcium and urinary excretion of hydroxyproline, without adversely affecting mineralisation.

5.2 Pharmacokinetic properties

Oral bioavailability is in the order of 2%.

Sodium clodronate is not metabolised. The volume of distribution is approximately 0.3L/kg. Elimination from serum is rapid, 75% of the dose is recovered unchanged in urine within 24 hours.

The elimination kinetics best fit a 3 compartment model. The first two compartments have relatively short half-lives. The third compartment is probably the skeleton.

Elimination half life is approximately 12 - 13 hours.

5.3 Preclinical safety data

Sodium clodronate shows relatively little toxicity either on single oral administration or after daily oral administration for a period of up to 6 months. In rats, a dose of 200mg/kg/day in the chronic toxicity test is at the limit of tolerability. In dogs, 40mg/kg/day chronically is within the tolerated range.

On daily administration of 500mg/kg for 6 weeks to rats, signs of renal failure with a clear rise in BUN, and initial liver parenchymal reaction with rises of SGOT, SGPT and AP occurred. No significant haematological changes were found in the toxicological investigations.

Investigations for mutagenic properties did not show any indication of mutagenic potency.

Reproduction toxicology investigations did not provide any indication of peri and post natal disorders, teratogenic damage or disorders of fertility.

It is not known if sodium clodronate passes into the mother's milk or through the placenta.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: Maize starch, Talc, Magnesium stearate, Sodium starch glycolate.

Capsule shell: Titanium dioxide (E171), Indigotin (E132), Gelatin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PVDC/aluminium blister packs:3 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 30, 60 or 120 capsules.

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Beacon Pharmaceuticals Limited

85 High Street, Tunbridge Wells, Kent TN1 1YG

8 MARKETING AUTHORISATION NUMBER(S)

PL 18157/0028

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

15 May 2007

10 DATE OF REVISION OF THE TEXT

28/11/2007

PATIENT INFORMATION LEAFLET

Patient Product Information

CLASTEON[®] 400mg capsules **Sodium clodronate**

What you should know about Clasteon (sodium clodronate)

Please read this carefully before you start to take your medicine. This leaflet provides a summary of the information available on your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

What is in your medicine?

The name of this medicine is Clasteon. Clasteon capsules are oblong, white and blue, and contain 400mg of sodium clodronate (as the tetrahydrate). Sodium clodronate is one of a group of medicines known as bisphosphonates. Clasteon capsules also contain talc, maize starch, magnesium stearate and sodium starch glycolate. The capsule shell is made of gelatin and contains titanium dioxide (E171), indigotin (E132) and printing ink.

Product Licence holder: Beacon Pharmaceuticals Ltd., Tunbridge Wells, TN1 1YG, UK

Clasteon is made and supplied in packs of 30, 60, or 120 capsules by Abiogen Pharma S.p.A., via Meucci 36, Ospedaletto – I-56014 Pisa - Italy.

What does your medicine do?

Your bones are losing too much calcium into your blood. This can make you ill. In some people, it can also cause bone pain or bone damage. You have been given Clasteon to stop this.

Before taking your medicine

- Do you have any kidney problems?
- Are you pregnant or breast feeding?
- Do you have stomach pain or bowel disturbance?
- Have you been given any antibiotic injections recently?
- Have you been allergic to similar medicines before?
- Are you taking any other medicines containing bisphosphonates?
- Have you ever had pain or swelling of your jaw, or are you having or planning to have dental treatment or surgery?

If the answer is YES to any of these questions do not take this medicine until you have talked to your doctor about it.

Take special care with your medicine

If you are having dental treatment or planning to have dental treatment or surgery, tell your dentist that you are being treated with Clasteon.

Taking your medicine

Clasteon is for use in adults only. It is important to take your medicine as your doctor has told you to. The label will tell you how many capsules to take. The usual dose is 4 capsules daily, but your doctor may tell you to take fewer or more capsules.

Swallow the capsules whole, with liquid (except milk). Do not take the capsules with food or within one hour before or one hour after food or milk. Please take the capsules even if you are not eating at present.

Please DO NOT take the capsules with milk. If Clasteon is taken with drinks containing milk it is harder for the medicine to enter the blood and so it does not work so well.

You do not have to change the food you eat

You can continue to have food and drinks containing milk, milk products, etc. as long as you do not take your capsules within one hour before or one hour after a meal.

For the same reason, DO NOT take Clasteon with antacid indigestion capsules or mineral supplements as these may also make the medicine work less well.

If you miss taking a dose do not worry, just take the next dose at the usual time.

If you or anyone else take an overdose there may be a feeling of sickness, or actual sickness (nausea and vomiting). You should contact your doctor at once.

After taking your medicine

This medicine may cause side effects in a few people. These can include a feeling of sickness (nausea) or diarrhoea. If this happens it may help if you take half the number of capsules in the morning and the rest in the evening, at bedtime.

A few people may have an allergy to sodium clodronate (itching, rash or shortness of breath/wheezing).

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

In a very few people, the kidneys may start to work less well than normal. Sometimes this can happen if Clasteon is taken

together with a non-steroidal anti-inflammatory drug (NSAID). In these cases, your doctor may wish to check your kidneys from time to time.

Your doctor may also wish to test your blood from time to time, to check that Clasteon is working correctly (calcium levels, white blood cells and hormones called LDH AND PTH).

Storing your medicine

- Keep this medicine in a safe place where children cannot reach it.
- Do not use this medicine after the expiry date shown on the label.
- If your doctor decides to stop the treatment, return any leftover capsules to the pharmacist. Only keep them if your doctor tells you to.
- REMEMBER this medicine is for you. Only a doctor can prescribe it for you. Never give it to others. It may harm them even if their symptoms are the same as yours.

Date of preparation/last review

June 2007



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LABELLING







