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

Degree of renal failure	Creatinine Clearance (ml/min)	Dose
Mild	50-80	1600mg daily (no dose reduction recommended)
Moderate	30-49	1200mg daily
Severe	10-29	800mg daily

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.

Atypical fractures of the femur

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

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

Fertility
In animal studies, clodronate did not cause foetal damage, but large doses decreased male fertility.
No clinical data on the effect of clodronate on fertility in humans are available. For use of clodronate in pregnancy and during lactation, see below.

Pregnancy
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).

Lactation
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:

System Organ Class	Common ≥ 1/100 to <1/10	Rare ≥ 1/10,000 to < 1/1,000	Frequency unknown
Metabolism and nutrition disorders	Asymptomatic hypocalcaemia.	Symptomatic hypocalcaemia. Increased levels of serum parathyroid hormone associated with decreased serum calcium levels. Increased levels of serum alkaline phosphatase.*	
Gastrointestinal disorders	Diarrhoea** Nausea** Vomiting**		
Hepatobiliary disorders	Levels of transaminases increased – usually within normal range.	Levels of transaminases increased to more than twice the normal range without associated abnormal hepatic function.	
Skin and subcutaneous tissue disorders		Hypersensitivity reaction manifesting as skin reaction e.g. pruritus, urticaria, exfoliative dermatitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm in patients with and without a previous history of asthma.	Impairment of respiratory function in patients with aspirin-sensitive asthma. Hypersensitivity reactions manifesting as respiratory disorder.
Renal and urinary disorders			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 NSAIDs, most often diclofenac.
Musculoskeletal and connective tissue disorders		Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction; from post-marketing experience) (see section 4.4).	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.
Eye Disorders			Uveitis has been reported with Sodium clodronate during post-marketing experience. Although the

			following reactions have been reported with other bisphosphonates; conjunctivitis, episcleritis and scleritis, only conjunctivitis has been reported for Sodium clodronate. This was in one patient concomitantly treated with another bisphosphonate. To date, episcleritis and scleritis (bisphosphonate class adverse reactions) have not been reported with Sodium clodronate

* 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 gastro-intestinal tolerance.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the following:
UK: Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.
IE: www.imb.ie, e-mail: imbpharmacovigilance@imb.ie or Tel: +353 1 6764971.
MT: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

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
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1312/12/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 November 2011

10 DATE OF REVISION OF THE TEXT

August 2014