

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

CLASTEON® 800 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1000 mg of disodium clodronate tetrahydrate, equivalent to 800 mg 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

Treatment of hypercalcemia due to malignancy.

Palliative treatment of osteolysis due to malignancy.

4.2 Posology and method of administration

Posology

Clodronate is mainly eliminated via the kidneys. Therefore, adequate fluid intake must be maintained during clodronate treatment.

Pediatric patients: Safety and efficacy in children have not been established.

Elderly patients:

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

CLASTEON® 800 mg tablets should be swallowed whole. A CLASTEON® 800 mg tablet may be divided into two to ease swallowing, but the halves have to be taken at the same time of administration. CLASTEON® 800 mg tablets must not be crushed or dissolved before intake.

A daily dose of 1600 mg should be taken as a single dose. 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 drugs.

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

Adult patients with normal renal function:

Treatment of hypercalcemia due to malignancy:

Intravenous clodronate treatment is recommended for the start of treatment in hypercalcemia. Subsequently, an oral dosage of 1600–3200 mg clodronate daily may be used. However, if oral therapy is used, a high starting dose of 2400–3200 mg should be used and, depending on the individual response, this can be reduced gradually to 1600 mg daily.

Treatment of osteolysis due to malignancy:

When oral therapy is used to treat increased bone resorption without hypercalcemia the recommended starting dose is 1600 mg daily. If clinically necessary, the dose may be increased, but is not recommended to exceed 3200 mg daily.

Patients with renal failure:

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

It is recommended that the clodronate dosage be reduced as follows:

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

*) No pharmacokinetic data are available in patients with renal failure with creatinine clearance below 10 ml/min for oral clodronate.

4.3 Contraindications

Sodium clodronate tablets are contraindicated in patients with severe renal failure where creatinine clearance less than 10 ml/min, except for short term use in the presence of purely functional renal insufficiency caused by elevated serum calcium levels.

Hypersensitivity to the active substance or to any of the excipients (listed in section 6.1) and in patients receiving concomitant treatment with other bisphosphonates.

Acute, severe inflammatory conditions of the gastrointestinal tract.

Pregnancy and lactation.

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.

Adequate fluid intake should be maintained during treatment.

Patients with renal impairment

Sodium clodronate should be administered with care to patients with renal impairment (see dose adjustment under "Patients with renal failure:"). Adequate fluid intake must be maintained during clodronate treatment. This is particularly important when administering clodronate to patients with hypercalcaemia or renal insufficiency. Renal function with serum creatinine, serum calcium and phosphate levels should be monitored before and during treatment.

In clinical trials, asymptomatic, reversible elevations of transaminases have occurred, without changes in other liver function tests. Monitoring of serum transaminases is advised (see also section 4.8).

Dental conditions and osteonecrosis of the jaw

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 both intravenous and oral 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.

Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Irritation of the upper gastrointestinal mucosa

Orally administered, mainly nitrogen-containing, bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when clodronate disodium is given to patients with active upper gastrointestinal problems (e.g. known Barrett's oesophagus, dysphagia, other oesophageal diseases, gastritis, duodenitis or ulcers).

Adverse experiences such as oesophagitis, oesophageal ulcers and oesophageal erosions, in some cases severe and requiring hospitalisation, rarely with bleeding or followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. The risk of severe oesophageal adverse experiences appears to be greater in patients who do not comply with the dosing instruction and/or who continue to take oral bisphosphonates after developing symptoms suggestive of oesophageal irritation. Patients should pay particular attention and be able to comply with the dosing.

Physicians should be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue clodronate disodium and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

While no increased risk was observed in controlled clinical trials there have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications.

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.

Excipients

This medicinal product contains 128.24 mg sodium per tablet, equivalent to 6.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of other bisphosphonates is contraindicated.

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.

Clodronate has been reported to be associated with renal dysfunction when used simultaneously with non-steroidal anti-inflammatory analgesics (NSAIDs), most often.

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 poorly soluble complexes with divalent metal ions. Therefore, clodronate should not be taken with calcium rich foods, antacids, and mineral supplements as these 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 is 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).

Breast-Feeding

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	Very Rare < 1/10,000	Frequency unknown
Immune system disorders		Allergic reaction	Bronchoconstriction	
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).	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).	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

				<p>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.</p>
Eye Disorders				<p>Uveitis has been reported with Sodium clodronate during post-marketing experience.</p> <p>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</p>

* 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

4.9 Overdose

Symptoms:

Increases in serum creatinine and renal dysfunction have been reported with high intravenous doses of clodronate. One case of acute renal failure and liver injury has been reported after accidental ingestion of 20,000 mg (50x400 mg) clodronate. It is theoretically possible that hypocalcaemia may develop up to 2 or 3 days following the overdose. Acute overdosage may be associated with gastrointestinal symptoms such as nausea and vomiting.

Management:

Management of overdose should be symptomatic. Adequate hydration should be ensured, and renal, hepatic 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 the 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. No other doses were studied. Furthermore, as stated by the authors: "*Bone uptake of clodronate and presumably clinical effectivity decreased with a dose reduction of clodronate*".

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.

Data from a bioequivalence study show that based on serum clodronate concentrations, the relative bioavailability of the tablet formulation is 91% (90% confidence interval 76-107%) of that of the capsule formulation. Urinary excretion of clodronate from one Clodronate 800 mg tablet is 92% (90% confidence interval 80-107%) of that of two Clodronate 400 mg capsules.

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 300 mg/kg respectively (0.5 to 2 times the maximum clinical dose based on body surface area, mg/m²), 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

Microcrystalline cellulose, sodium starch glycolate (type A), pregelatinized starch, magnesium stearate, colloidal anhydrous silica.

The tablet coating contains: polyvinyl alcohol, titanium dioxide (E171), macrogol (E1521) and talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C.

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

BioAvenir Ltd., David HaMelech St 1, Herzeliya Pituach

8 MARKETING AUTHORISATION NUMBER

158-03-34600

9 MANUFACTURER

Aboigen Pharma S.P.A, Via Meucci 36, 56121 Ospedaletto - Pisa, Italy

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