4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Intravenous use
  Treatment of hypercalcemia due to malignancy.

- Oral use
  Treatment of hypercalcemia due to malignancy.
  Treatment of osteolysis due to malignancy.
  Reduction of occurrence of bone metastases in primary breast cancer.

4.2 Posology and method of administration

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

- Children
  Safety and efficacy in pediatric patients have not been established.

- Elderly
  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.

4.2.1 Intravenous infusion (only for short-term therapy)

Adequate hydration must be ensured during intravenous treatment with Bonefos.

The length of time that a clinically acceptable serum calcium level is maintained after infusion of clodronate varies considerably from patient to patient. The infusion may be repeated if necessary to control the serum calcium level or, alternatively, treatment with oral clodronate may be appropriate.

- Adult patients with normal renal function
  Clodronate is given as an intravenous infusion of 300 mg (one 5 ml ampoule)/day diluted into 500 ml of either saline (sodium chloride 9 mg/ml) or 5% glucose (50 mg/ml) solution. The prepared solution shall be infused over a period of a minimum of two hours on successive days until normocalcemia is achieved, which usually happens within five days. Such therapy should normally not be continued for more than seven days. Alternatively, the dose of 1500 mg clodronate can be given as a single dose, diluted in a volume of 500 ml as recommended above, with an infusion time of four hours.

- Patients with renal failure
  It is recommended that the clodronate dosage to be infused be reduced as follows:

<table>
<thead>
<tr>
<th>Degree of Renal Failure: Creatinine Clearance, ml/min</th>
<th>Reduction in dosage, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-80</td>
<td>25</td>
</tr>
<tr>
<td>12-50</td>
<td>25-50</td>
</tr>
<tr>
<td>&lt;12</td>
<td>50</td>
</tr>
</tbody>
</table>
It is recommended that 300 mg clodronate be infused prior to hemodialysis and that the dose be reduced by 50% on non-dialysis days, and limit the treatment schedule to 5 days. It should be noted that peritoneal dialysis removes clodronate poorly from the circulation.

4.2.2 Oral

Bonefos capsules and 400 mg tablets should be swallowed whole. A Bonefos 800 mg tablet may be divided into two to ease swallowing, but the halves have to be taken at the same time of administration. Bonefos tablets should 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 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.

- Adult patients with normal renal function
  
  Treatment of hypercalcemia due to malignancy

  Intravenous clodronate is recommended for the treatment of hypercalcemia 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 normocalcemia.

  Treatment of osteolysis due to malignancy

  When oral therapy is used to treat increased bone resorption without hypercalcemia the dosage is individual. 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.

Reduction of occurrence of bone metastases in primary breast cancer

The recommended dose is 1600 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:

<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 ml/min</td>
<td>1600 mg daily (no dose reduction recommended)</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-50 ml/min</td>
<td>1200 mg/daily</td>
</tr>
<tr>
<td>Severe *</td>
<td>&lt;30 ml/min</td>
<td>800 mg/daily</td>
</tr>
</tbody>
</table>

* No pharmacokinetic data are available in patients with renal failure with creatinine clearance below 10 ml/min for oral clodronate. Use in such instances should be avoided except for short term
use in the presence of purely functional renal insufficiency caused by elevated serum calcium levels.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Concomitant treatment with other bisphosphonates.

4.4 Special warnings and precautions for use

Adequate fluid intake must be maintained during clodronate treatment. This is particularly important when administering clodronate as intravenous infusion and in patients with hypercalcemia or renal failure.

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).

Clodronate should be used with caution in patients with renal failure (see dose adjustment under “Dosage and method of administration”).

Intravenous administration of doses notably higher than those recommended may cause severe renal damage, especially if the infusion rate is too high.

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 bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor dental hygiene) and invasive dental procedures should be avoided while patients are being treated with bisphosphonates.

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

Bonefos 60 mg/ml concentrate for solution for infusion contains 53 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

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 with other bisphosphonates is contraindicated.

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

Due to increased risk of hypocalcemia, caution should be taken when using clodronate together with aminoglycosides.

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

Clodronate forms poorly soluble complexes with divalent cations. Therefore, clodronate should not be administered intravenously with solutions containing divalent cations (e.g. Ringer’s solution). In addition clodronate tablets/capsules should not be taken with food or drugs containing divalent cations (e.g. antacids or iron preparations).

4.6 Fertility, pregnancy and lactation

4.6.1 Fertility

In animal studies, clodronate did not cause fetal 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 sections 4.6.2 and 4.6.3.

4.6.2 Pregnancy

Although in animals clodronate passes through the placental barrier, it is not known if it passes into the fetus in humans. Furthermore, it is not known if clodronate can cause fetal damage or affect reproduction in humans. There are only limited amount of data from the use of clodronate in pregnant women. Bonefos is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

4.6.3 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 Bonefos.

4.7 Effects on ability to drive and use machines

No known effects on the ability to drive or use machines.

4.8 Undesirable effects

The most common reported drug reaction is diarrhea which is usually mild and occurs more commonly with higher doses.

These adverse reactions may occur in connection with both oral and intravenous treatment, although the frequency of reactions may differ.
### Post-marketing experience

- Respiratory, thoracic and mediastinal disorders
  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 especially after rapid intravenous infusion of high doses of clodronate (for dosage instructions see section 4.2 under “Intravenous infusion” chapter “Patients with renal failure”).

Single cases of renal failure, in rare cases with fatal outcome have been reported especially with concomitant use of NSAIDs, most often diclofenac.

- Musculoskeletal and connective tissue disorders:
  Isolated cases of osteonecrosis of the jaw have been reported, primarily in patients who were previously treated with amino-bisphosphonates like zoledronate and pamidronate (see also section 4.4). Severe bone, joint, and/or muscle pain has been reported in patients taking Bonefos. However, such reports have been infrequent and in randomised placebo controlled studies no differences are apparent between placebo and Bonefos treated patients. The onset of symptoms varied from days to several months after starting Bonefos.

During post-marketing experience the following reactions have been reported (frequency rare): atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

### 4.9 Overdose

- Symptoms
Increases in serum creatinine and renal dysfunction have been reported with high intravenous doses of clodronate.

- **Treatment**
  Treatment of overdose should be symptomatic. Adequate hydration should be ensured, and renal function and serum calcium should be monitored.