1. NAME OF THE MEDICINAL PRODUCT

Aclasta 5 mg solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle with 100 ml of solution contains 5 mg zoledronic acid anhydrous, corresponding to 5.330 mg zoledronic acid monohydrate.

One ml solution contains 0.05 mg zoledronic acid anhydrous corresponding to 0.0533 mg zoledronic acid monohydrate.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Paget’s disease of the bone.

4.2 Posology and method of administration

Aclasta should be prescribed only by physicians with experience in treatment of Paget’s disease of the bone.

The recommended dose is one intravenous infusion of 5 mg zoledronic acid (anhydrous) in 100 ml aqueous solution administered via a vented infusion line given at a constant infusion rate. The infusion time must not be less than 15 minutes.

For information on the infusion of Aclasta, see section 6.6.

Patients must be appropriately hydrated prior to administration of Aclasta. This is especially important for patients receiving diuretic therapy.

Adequate vitamin D intake is recommended in association with Aclasta administration. In addition, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured in patients with Paget’s disease for at least 10 days following Aclasta administration (see section 4.4).

Retreatment of Paget’s disease: specific retreatment data are not available. After a single treatment with Aclasta in Paget’s disease, an extended remission period is observed in responding patients (see section 5.1).

Patients with renal impairment (see section 4.4)
Use of Aclasta in patients with creatinine clearance < 30 ml/min is not recommended due to lack of adequate clinical experience in this population.
No dose adjustment is necessary in patients with creatinine clearance $\geq 30$ ml/min.

**Patients with hepatic impairment**
No dose adjustment is required (see section 5.2).

**Elderly patients (≥ 65 years)**
No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly patients and younger subjects.

**Children and adolescents**
Aclasta has not been tested in children and adolescents and therefore should not be used in these age groups.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Aclasta is contraindicated for patients with hypocalcaemia (see section 4.4).

Aclasta is contraindicated during pregnancy and in breast-feeding women (see section 4.6).

### 4.4 Special warnings and special precautions for use

The dose of 5 mg zoledronic acid must be administered over at least 15 minutes.

Aclasta is not recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min) due to lack of adequate clinical experience in this population.

Patients must be appropriately hydrated prior to administration of Aclasta. This is especially important for patients receiving diuretic therapy. Caution is indicated when Aclasta is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration), see section 4.5.

Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta (see section 4.3). Other disturbances of mineral metabolism must also be effectively treated.

Elevated bone turnover is a characteristic of Paget’s disease of the bone. Due to the rapid onset of effect of zoledronic acid on bone turnover, transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days after infusion of Aclasta (see section 4.8). Adequate vitamin D intake is recommended in association with Aclasta administration. In addition, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured in patients with Paget's disease for at least 10 days following Aclasta administration (see section 4.2).

Patients should be informed about symptoms of hypocalcaemia and receive adequate clinical monitoring during the period of risk.

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

Specific drug-drug interaction studies have not been conducted with zoledronic acid. Zoledronic acid is not systemically metabolised and does not affect human cytochrome P450 enzymes *in vitro* (see section 5.2). Zoledronic acid is not highly bound to plasma proteins (approximately 56% bound) and interactions resulting from displacement of highly protein-bound drugs are therefore unlikely.
Zoledronic acid is eliminated by renal excretion. Caution is indicated when Aclasta is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration).

4.6 Pregnancy and lactation

There are no adequate data on the use of zoledronic acid in pregnant women. Studies in animals with zoledronic acid have shown reproductive toxicological effects including malformations (see section 5.3). The potential risk for humans is unknown. It is not known whether zoledronic acid is excreted into human breast milk. Aclasta is contraindicated during pregnancy and in breast-feeding women (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Intravenous administration of Aclasta has been most commonly associated with the following symptoms suspected to be related to study drug and which usually occur within 3 days following Aclasta administration: flu-like symptoms (11.9%), fever (6.8%), headache (6.2%), nausea (5.6%), bone pain (4.5%), myalgia (6.2%) and arthralgia (4.0%). The majority of these symptoms resolve within 4 days of the event onset.

Very common (>1/10) and common (≥1/100, <1/10) adverse reactions suspected (investigator assessment) to be drug related and occurring more than once in Paget’s patients receiving Aclasta over a 6-month study period are listed by system organ class in Table 1.

Table 1 Adverse reactions suspected* to be drug related occurring more than once in Paget’s patients receiving Aclasta over a 6-month follow-up period

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Hypocalcaemia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache, lethargy</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Common</td>
<td>Dyspnoea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Diarrhoea, nausea, dyspepsia</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Common</td>
<td>Bone pain, arthralgia, myalgia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>Flu-like symptoms</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Pyrexia, rigors, fatigue, pain, asthenia</td>
</tr>
</tbody>
</table>

* Investigator assessment.

Laboratory findings: Early, transient decreases in serum calcium and phosphate levels have been observed commonly. Hypocalcaemia may be symptomatic in some patients (see section 4.2 and section 4.4).

Class-effects:

Renal dysfunction: Renal dysfunction has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise or additional risk factors (e.g. oncology patients with chemotherapy, concomitant nephrotoxic medications, severe dehydration, etc).
Iritis/uveitis/episcleritis/conjunctivitis: Cases of iritis, uveitis and episcleritis have been reported in patients treated with bisphosphonates, although no cases were reported in the Paget’s disease studies. Conjunctivitis has been reported in patients treated with zoledronic acid.

Osteonecrosis of the jaw: Osteonecrosis of the jaw (ONJ) has been reported primarily in patients with cancer receiving treatment regimens including bisphosphonates. Osteonecrosis of the jaw has multiple well documented risk factors including a diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, local infection including osteomyelitis, and the majority of reported cases have been associated with dental procedures such as tooth extractions. A causal relationship between bisphosphonate use and ONJ has not been established. ONJ has not been observed in the Paget’s disease clinical studies.

4.9 Overdose

There is no experience of acute intoxication with Aclasta. Patients who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an intravenous infusion of calcium gluconate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bisphosphonate, ATC code: M05 BA 08

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone. Intravenously administered zoledronic acid is rapidly distributed to bone and, like other bisphosphonates, localises preferentially at sites of bone resorption. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase, but this does not exclude other mechanisms. In long-term studies in oestrogen-deficient animals, zoledronic acid inhibited bone resorption and increased bone mass at doses ranging from 0.03 to 8 times the equivalent human dose. A dose-dependent increase in bone strength and other bone mechanical properties was demonstrated. At doses 0.8 to 8 times the human equivalent, bone mechanical properties were improved in ovariectomised animals relative to non-ovariectomised controls. Histomorphometric analyses showed the typical response of bone to an anti-resorptive agent with a dose-dependent reduction in osteoclastic activity and activation frequency of new remodelling sites in both trabecular and Haversian bone. Continuing bone remodelling was observed in bone samples from all animals treated with clinically relevant doses of zoledronic acid. There was no evidence of a mineralising defect, no aberrant accumulation of osteoid, and no woven bone in treated animals.

Paget’s disease of the bone: Aclasta was studied in male and female patients aged above 30 years with primarily mild to moderate Paget’s disease of the bone (median serum alkaline phosphatase level 2.6–3.0 times the upper limit of the age-specific normal reference range at the time of study entry) confirmed by radiographic evidence.

The efficacy of one infusion of 5 mg zoledronic acid versus daily doses of 30 mg risedronate for 2 months was demonstrated in two 6-month comparative trials. Therapeutic response was defined as either normalisation of serum alkaline phosphatase (SAP) or a reduction of at least 75% from baseline in total SAP excess at the end of 6 months. SAP excess was defined as the difference between the measured level and midpoint of the normal range.
In both trials Aclasta demonstrated a superior and more rapid therapeutic response compared with
risedronate as evidenced by biochemical markers of formation (SAP, serum N-terminal propeptide of
type I collagen (P1NP)) and resorption (serum CTx 1 (cross-linked C-telopeptides of type I collagen)
and urine α-CTx).

In combined data from both trials, after 2 months, Aclasta showed a superior therapeutic response of
90% (158/176) and SAP normalisation rate of 63% (111/176) compared to 47% (81/171) and 26%
(45/171) respectively for risedronate (all p<0.001). After 6 months, Aclasta showed 96% (169/176) and
89% (156/176) response and normalisation rates compared to 74% (127/171) and 58% (99/171) for
risedronate (all p<0.001).

In the pooled results, a similar decrease in pain severity and pain interference scores relative to baseline
were observed over 6 months for Aclasta and risedronate.

The therapeutic response by subgroup is presented in Table 2.

Table 2 Proportion of patients who achieved therapeutic response at 6 months by disease
factors

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Aclasta n/N (Proportion)</th>
<th>Risedronate n/N (Proportion)</th>
<th>p-value for treatment difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3xULN</td>
<td>87/90 (0.97)</td>
<td>74/99 (0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ 3xULN</td>
<td>82/86 (0.95)</td>
<td>53/72 (0.74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Last Paget’s therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral bisphos.*</td>
<td>53/55 (0.96)</td>
<td>33/60 (0.55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IV bisphos.</td>
<td>22/25 (0.88)</td>
<td>21/26 (0.81)</td>
<td>0.4590</td>
</tr>
<tr>
<td>Clodronate</td>
<td>6/6 (1.00)</td>
<td>2/2 (1.00)</td>
<td>NA</td>
</tr>
<tr>
<td>Others</td>
<td>8/8 (1.00)</td>
<td>6/7 (0.86)</td>
<td>0.2733</td>
</tr>
<tr>
<td>No previous therapy</td>
<td>80/82 (0.98)</td>
<td>65/76 (0.86)</td>
<td>0.0075</td>
</tr>
</tbody>
</table>

SAP = serum alkaline phosphatase. ULN = upper limit of normal. A therapeutic response is defined as
normalisation of SAP or a reduction of ≥ 75% from baseline in SAP excess. N = number of patients
with baseline and at least one post-baseline SAP measurements. n = number of patients with therapeutic
response at visit.

*Including previous treatment with risedronate

Patients who were classified as responders at the end of the 6 month core study were eligible to enter an
extended follow-up period. Of the 143 Aclasta-treated patients and 107 risedronate-treated patients who
entered an extended observation study, after a median duration of follow-up of 18 months from time of
dosing, 141 Aclasta-treated patients maintained their therapeutic response compared to 71 risedronate-
treated patients.

The cumulative rate of maintaining therapeutic response in the extended follow-up period is displayed in
Figure 1.

Figure 1 Cumulative rate of maintaining therapeutic response over time
Time to first loss of therapeutic response: the occurrence of an SAP level that no longer meets the criteria of a therapeutic response (less than 75% reduction in SAP excess and/or SAP above the upper limit of the normal range).

Bone histology was evaluated in 7 patients with Paget's disease 6 months after treatment with 5 mg zoledronic acid. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodelling and no evidence of mineralisation defects. These results were consistent with biochemical marker evidence of normalisation of bone turnover.

5.2 Pharmacokinetic properties

Single and multiple 5 and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid in 64 patients yielded the following pharmacokinetic data, which were found to be dose independent.

After initiation of the zoledronic acid infusion, plasma concentrations of the active substance increased rapidly, achieving their peak at the end of the infusion period, followed by a rapid decline to < 10% of peak after 4 hours and < 1% of peak after 24 hours, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak levels.

Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{1/2\alpha}$ 0.24 and $t_{1/2\beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2\gamma}$ 146 hours. There was no accumulation of the active substance in plasma after multiple doses given every 28 days. Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Over the first 24 hours, 39 ± 16% of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue. From the bone tissue it is released very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.04 ± 2.5 l/h, independent of dose, and unaffected by gender, age, race or body weight. The inter- and intra-subject variation for plasma clearance of zoledronic acid was shown to be 36% and 34%, respectively. Increasing the infusion time from 5 to 15 minutes caused a
30% decrease in zoledronic acid concentration at the end of the infusion, but had no effect on the area under the plasma concentration versus time curve.

No specific drug-drug interaction studies have been conducted with zoledronic acid. Since zoledronic acid is not metabolised in humans and the substance was found to have little or no capacity as a direct-acting and/or irreversible metabolism-dependent inhibitor of P450 enzymes, zoledronic acid is unlikely to reduce the metabolic clearance of substances which are metabolised via the cytochrome P450 enzyme systems. Zoledronic acid is not highly bound to plasma proteins (approximately 56% bound) and binding is concentration independent. Therefore, interactions resulting from displacement of highly protein-bound drugs are unlikely.

Special populations (see section 4.2)

The renal clearance of zoledronic acid was correlated with creatinine clearance, renal clearance representing 75 ± 33% of the creatinine clearance, which showed a mean of 84 ± 29 ml/min (range 22 to 143 ml/min) in the 64 patients studied. Small observed increases in AUC_{(0-24hr)} by about 30% to 40% in mild to moderate renal impairment, compared to a patient with normal renal function, and lack of accumulation of drug with multiple doses irrespective of renal function, suggest that dose adjustments of zoledronic acid in mild (Cl_{cr} = 50–80 ml/min) and moderate (Cl_{cr} = 30–50 ml/min) renal impairment are not necessary. As only limited data are available in severe renal impairment (creatinine clearance < 30 ml/min), no dosing recommendations are possible for this population.

5.3 Preclinical safety data

Acute toxicity

The highest non-lethal single intravenous dose was 10 mg/kg body weight in mice and 0.6 mg/kg in rats. In the single-dose dog infusion studies, 1.0 mg/kg (6 fold the recommended human therapeutic exposure based on AUC) administered over 15 minutes was well tolerated with no renal effects.

Subchronic and chronic toxicity

In the intravenous infusion studies, renal tolerability of zoledronic acid was established in rats when given 0.6 mg/kg as 15-minute infusions at 3-day intervals, six times in total (for a cumulative dose that corresponded to AUC levels about 6 times the human therapeutic exposure) while five 15-minute infusions of 0.25 mg/kg administered at 2–3-week intervals (a cumulative dose that corresponded to 7 times the human therapeutic exposure) were well tolerated in dogs. In the intravenous bolus studies, the doses that were well-tolerated decreased with increasing study duration: 0.2 and 0.02 mg/kg daily was well tolerated for 4 weeks in rats and dogs, respectively but only 0.01 mg/kg and 0.005 mg/kg in rats and dogs, respectively, when given for 52 weeks.

Longer-term repeat administration at cumulative exposures sufficiently exceeding the maximum intended human exposure produced toxicological effects in other organs, including the gastrointestinal tract and liver, and at the site of intravenous administration. The clinical relevance of these findings is unknown. The most frequent finding in the repeat-dose studies consisted of increased primary spongiosa in the metaphyses of long bones in growing animals at nearly all doses, a finding that reflected the compound’s pharmacological antiresorptive activity.

Reproduction toxicity

Teratology studies were performed in two species, both via subcutaneous administration. Teratogenicity was observed in rats at doses ≥ 0.2 mg/kg and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg body weight) tested in rats. No teratological or embryo/foetal effects were observed in rabbits, although maternal toxicity was marked at 0.1 mg/kg due to decreased serum calcium levels.

Mutagenicity and carcinogenic potential

Zoledronic acid was not mutagenic in the mutagenicity tests performed and carcinogenicity testing did not provide any evidence of carcinogenic potential.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol  
Sodium citrate  
Water for injections

6.2 Incompatibilities

Aclasta must not be allowed to come into contact with any calcium-containing solutions. Aclasta must not be mixed or given intravenously with any other medicinal products.

6.3 Shelf life

Unopened bottle: 30 months  
After opening: 24 hours at 2°C - 8°C

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

The unopened bottle does not require any special storage conditions.

6.5 Nature and contents of container

100 ml transparent plastic (cycloolefinic polymer) bottle closed with a fluoro-polymer coated bromobutyl rubber stopper and an aluminium/polypropylene cap with a flip component.

Aclasta is supplied as packs containing one bottle.

6.6 Instructions for use and handling

For single use only. Any unused solution should be discarded. Only clear solution free from particles and discoloration should be used.

If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during the preparation of the infusion.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited  
Wimblehurst Road  
Horsham  
West Sussex, RH12 5AB  
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURING AUTHOURISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release:

Novartis Pharma Produktions GmbH
Oeflingerstrasse 44, D-79664 Wehr/Baden
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription. (See Annex I: Summary of Product Characteristics, 4.2)

• OTHER CONDITIONS

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING FOLDING BOX AND BOTTLE LABEL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
</tbody>
</table>
| Aclasta 5 mg solution for infusion  
Zoledronic acid |
| **2. STATEMENT OF ACTIVE SUBSTANCE(S)** |
| One bottle with 100 ml solution contains 5 mg of zoledronic acid anhydrous, corresponding to 5.330 mg zoledronic acid monohydrate. |
| **3. LIST OF EXCIPIENTS** |
| Mannitol, sodium citrate and water for injections. |
| **4. PHARMACEUTICAL FORM AND CONTENTS** |
| One bottle with 100 ml solution for infusion. |
| **5. METHOD AND ROUTE(S) OF ADMINISTRATION** |
| Intravenous use.  
For single use only.  
Read the package leaflet before use. |
| **6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN** |
| Keep out of the reach and sight of children. |
| **7. OTHER SPECIAL WARNING(S), IF NECESSARY** |
|  |
| **8. EXPIRY DATE** |
| EXP {MM/YYYY}  
After opening: 24 hours at 2°C - 8°C. |
| **9. SPECIAL STORAGE CONDITIONS** |
| The unopened bottle does not require any special storage conditions. |
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

   Marketing Authorisation Holder:  
   Novartis Europharm Limited  
   Wimblehurst Road  
   Horsham  
   West Sussex, RH12 5AB  
   United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

   EU/0/00/000/000

13. **MANUFACTURER'S BATCH NUMBER**

   Lot {number}

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**
B. PACKAGE LEAFLET
1. WHAT ACLASTA IS AND WHAT IT IS USED FOR

Aclasta comes in 100 ml plastic bottles as a ready-to-use solution for infusion.

Aclasta is supplied in packs containing one bottle.

Aclasta is given as a single infusion into a vein by a doctor or nurse. It belongs to a group of medicines called bisphosphonates and is used to treat Paget’s disease of the bone.

Paget’s disease of the bone: It is normal that old bone breaks down and is replaced with new bone material. This process is called remodelling. In Paget’s disease, the bone material breaks down too much, and new bone material grows too quickly and in a disordered way. The bone material produced is weaker than normal. If the disease is not treated, bones may become deformed and painful, and may break. Aclasta works by returning the bone remodelling process to normal, and restoring strength to the bone.
2. BEFORE YOU ARE GIVEN ACLASTA

Make sure you drink enough fluids (at least one or two glasses) before and after the treatment with Aclasta, as directed by your doctor. This will help to prevent dehydration.

Follow all instructions given to you by your doctor carefully before you are given Aclasta.

You should not be given Aclasta:
- if you are allergic (hypersensitive) to zoledronic acid or any of the other ingredients of Aclasta.
- if you have hypocalcaemia (this means that the levels of calcium in your blood are too low).
- if you are pregnant or plan to become pregnant.
- if you are breast-feeding.

Tell your doctor before you are given Aclasta:
- if you have a kidney problem, or used to have one.

Pregnancy
You should not be given Aclasta if you are pregnant or plan to become pregnant.

Ask your doctor, pharmacist or nurse for advice before taking any medicine.

Breast-feeding
You should not be given Aclasta if you are breast-feeding.

Ask your doctor, pharmacist or nurse for advice before taking any medicine.

Elderly patients (age 65 years and over)
Aclasta can be given to older patients.

Children and adolescents
Aclasta is not recommended for anyone under 18 years of age. The use of Aclasta in children and adolescents has not been studied.

Driving and using machines
Aclasta has no known effects on the ability to drive or use machines.

Taking other medicines
Tell your doctor, pharmacist or nurse if you are taking or have recently taken any other medicines, including any you have bought without a prescription. It is especially important for your doctor to know if you are taking any medicines known to be harmful to your kidneys.

3. HOW ACLASTA IS GIVEN

The usual dose is 5 mg, given to you as one single infusion into a vein by your doctor or nurse. The infusion will take at least 15 minutes. As Aclasta works for a long time, you may not need another dose of Aclasta for a year or longer.

Follow carefully all instructions given to you by your doctor or nurse.
Your doctor may advise you to take calcium and vitamin D supplements for at least the first ten days after being given Aclasta. It is important that you follow this advice carefully in order to reduce the risk of hypocalcaemia (too low blood calcium) in the period after the infusion. Your doctor will inform you regarding the symptoms associated with hypocalcaemia.
4. POSSIBLE SIDE EFFECTS

Like all medicines, Aclasta can have side effects. In most cases, no specific treatment is required.

Common side effects – likely to affect between 1 and 10 in every 100 patients – are:
- Fever and chills
- Tiredness, weakness
- Headache
- Shortness of breath
- Diarrhoea, indigestion or feeling sick
- Pain in your muscles, bones or joints
- Symptoms due to low blood calcium, such as muscle spasms, or numbness, or a tingling sensation especially in the area around the mouth

If you notice any of these side effects, tell your doctor.

If you notice any side effects not mentioned in this leaflet, please inform your doctor, pharmacist or nurse.

5. STORING ACLASTA

Your doctor, pharmacist or nurse knows how to store Aclasta properly. See also the section “Information for the health care professional” at the end of this leaflet.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Novartis (Hellas) A.E.B.E.

Österreich
Novartis Pharma GmbH
INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for medical or healthcare professionals only:

The dose of 5 mg of zoledronic acid must be administered over at least 15 minutes. Aclasta is not recommended for patients with severe renal impairment (creatinine clearance < 30 ml/min) due to lack of adequate clinical experience in this population. Patients must be appropriately hydrated prior to administration of Aclasta, this is especially important for patients receiving diuretic therapy. Caution is indicated when Aclasta is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration). Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta. Other disturbances of mineral metabolism must also be effectively treated. Elevated bone turnover is a characteristic of Paget’s disease of the bone. Due to the rapid onset of effect of zoledronic acid on bone turnover, transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days after infusion of Aclasta (see section 4.8). Adequate vitamin D intake is recommended in association with Aclasta administration. In addition, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured in patients with Paget's disease for at least 10 days following Aclasta administration (see section 4.2).

Patients should be informed about symptoms of hypocalcaemia and receive adequate clinical monitoring during the period of risk.

How to prepare and administer Aclasta

- Aclasta 5 mg solution for infusion is ready for use.

For single use only. Any unused solution should be discarded. Only clear solution free from particles and discoloration should be used. Aclasta must not be mixed or given intravenously with any other medication and must be given through a separate vented infusion line at a constant infusion rate. The infusion time must not be less than 15 minutes. Aclasta must not be allowed to come into contact with any calcium-containing solutions. If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during preparation of the infusion. The infusion must be conducted according to standard medical practice.

How to store Aclasta

- Keep Aclasta out of the reach and sight of children.
- Do not use Aclasta after the expiry date stated on the carton and bottle.
- The unopened bottle does not require any special storage conditions.
- After opening the bottle, the product should be used immediately in order to avoid microbial contamination. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C. Allow the refrigerated solution to reach room temperature before administration.