PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

ACLASTA 5 mg/100 mℓ (solution for infusion)

COMPOSITION:

One bottle with 100 mℓ solution contains 5 mg zoledronic acid anhydrous corresponding to 5,330 mg zoledronic acid monohydrate.

List of excipients: Mannitol, sodium citrate, water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A 34 Other

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Mechanism of action:

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 localises preferentially at sites of high bone turnover. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase, but this does not exclude other mechanisms. The relatively long duration of action of zoledronic acid is attributable to its high binding affinity for the active site of farnesyl pyrophosphate (FPP) synthase and its strong binding affinity to bone mineral.

Pharmacodynamic effects:

Osteoporosis:

Zoledronic acid treatment reduced the rate of bone turnover from elevated post- menopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at 12 weeks. Thereafter bone markers stabilized within the pre- menopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing. In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting bone formation, mineralisation or the mechanical properties of 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.

Pharmacokinetic properties:

After initiation of a zoledronic acid infusion, the plasma concentration of the active substance increases rapidly, achieving the peak concentration at the end of the infusion period. This is 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 $t_{½\alpha}$ 0.24 and $t_{½\beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½\gamma}$ hours. There was no accumulation of the active substance in plasma after multiple doses given every 28 days. The early disposition phases (alpha and beta, with $t_{½}$ values above) presumably represent rapid uptake into bone and excretion via the kidneys. 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.

Special populations:

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 $AUC_{(0\text{-}24hr)}$, 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 to 80 mℓ /min) and moderate (Cl_{cr} = 30 to 50 mℓ/min) renal impairment are not necessary.

The use of ACLASTA in patients with creatinine clearance <35 mℓ/min is not recommended due to limited clinical safety data in such (see *"Warnings and special precautions").*

No dose adjustment is necessary in patients with creatinine clearance 35 mℓ/min.

INDICATIONS

Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures and to increase bone mineral density.

In patients with a recent low trauma hip fracture, ACLASTA reduces the incidence of new clinical fractures.

Treatment of osteoporosis in men.

Treatment of glucocorticoid-induced osteoporosis. Treatment of Paget's disease of bone.

CONTRA-INDICATIONS

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

Hypocalcaemia (see "*Warnings and special precautions*").

Pregnancy and lactation (see "*Pregnancy and lactation").*

Severe impairment of renal function (creatinine clearance of < 35 mℓ /min): the safety and efficacy in patients with severe renal impairment have not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

General:

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

Patients treated with another bisphosphonate should not receive ACLASTA.

Patients must be appropriately hydrated prior to administration of ACLASTA. This is especially important in the elderly and for patients receiving diuretic therapy.

Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with ACLASTA (see "*Contra-indications").* Other disturbances of mineral metabolism must also be effectively treated (e.g. diminished parathyroid reserve; thyroid surgery, parathyroid surgery, intestinal calcium malabsorption). Medical practitioners should consider clinical monitoring for these patients.

Renal impairment:

ACLASTA is contra-indicated for patients with renal impairment. (creatinine clearance < 35 mℓ /min) due to limited clinical safety data in such patients (see "*contra-indications").* Patients should have serum creatinine measured before receiving ACLASTA.

Renal dysfunction:

Renal dysfunction has been observed following the administration of ACLASTA, especially in patients with pre-existing renal compromise or additional risk factors (e.g. oncology patients with chemotherapy, concomitant nephrotoxic medications and severe dehydration).

Renal failure requiring dialysis has rarely occurred in patients with underlying renal impairment.

The following precautions should be taken into account to minimize the risk of renal adverse reactions:

- ACLASTA should not be used in patients with severe renal impairment (creatinine clearance < 35 mℓ /min) due to limited clinical safety data in such patients (see "*Pharmacokinetics").* ACLASTA should be used with caution when concomitantly used with other medicinal products that could impact renal function (see "*Interactions").*
- Serum creatinine should be measured before each ACLASTA dose. Transient increase in serum creatinine may be greater in patients with underlying impaired renal function; interim monitoring of serum creatinine should be considered in at- risk patients.

- Patients, especially those receiving diuretic therapy, should be appropriately hydrated prior to administration of ACLASTA.
- A single dose of ACLASTA should not exceed 5 mg and the duration of infusion should not be less than 15 minutes (see "*Dosage and Directions for use").*

Calcium and Vitamin D Supplementation: Treatment of Postmenopausal Osteoporosis:

Adequate supplemental calcium and vitamin D intake is important in men and women with osteoporosis if dietary intake is inadequate.

Prevention of Clinical Fractures after a hip fracture:

Supplemental calcium and vitamin D intake is recommended for patients treated to prevent clinical fractures after a hip fracture.

Treatment of Paget's disease of bone:

Elevated bone turnover is a characteristic of Paget's disease of 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 "*Side effects*"). 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. Patients should be informed about symptoms of hypocalcaemia. Medical practitioners should consider clinical monitoring for patients at risk.

Musculoskeletal pain:

Severe and occasionally incapacitating bone, joint, and/or muscle pain have been infrequently reported in patients taking ACLASTA.

Osteonecrosis of the jaw:

Osteonecrosis of the jaw (ONJ): Osteonecrosis of the jaw has been reported predominantly in cancer patients treated with bisphosphonates, including ACLASTA. Many of these patients were

also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis. A dental examination with appropriate preventive dentistry should be considered prior to treatment with ACLASTA in patients with concomitant risk factors (e.g. cancer, chemotherapy, 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 ACLASTA therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of ACLASTA treatment reduces the risk of osteonecrosis of the jaw. The clinical judgement of the treating medical practitioner should guide the management plan of each patient based on individual benefit/risk assessment.

INTERACTIONS

Specific medicine interaction studies have not been conducted with ACLASTA. ACLASTA is not systemically metabolised and does not affect human cytochrome P450 enzymes *in vitro* (see "*Pharmacokinetic properties").*

ACLASTA is not highly bound to plasma proteins (approximately 43- 55 % bound) and interactions resulting from displacement of highly protein-bound medicines are therefore unlikely.

ACLASTA is eliminated by renal excretion.

Medicines that could impact renal function:

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).

Medicines primarily excreted by the kidney:

In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidneys may increase.

Pharmaceutical incompatibilities:

ACLASTA solution for infusion must not be allowed to come into contact with any calcium-containing solutions.

PREGNANCY AND LACTATION:

ACLASTA is contraindicated during pregnancy and in breast-feeding women (see "*Contra-indications*").

DOSAGE AND DIRECTIONS FOR USE:

General:

The incidence of post-dose symptoms occurring within the first three days after administration of ACLASTA can be reduced with the administration of paracetamol or ibuprofen shortly following ACLASTA administration.

Patients must be appropriately hydrated prior to administration of ACLASTA. This is especially important in the elderly and for patients receiving diuretic therapy (see *"Warnings and special precautions").*

Treatment of Postmenopausal Osteoporosis:

For the treatment of postmenopausal osteoporosis the recommended dose is a single intravenous infusion of 5 mg infusion of ACLASTA administered once a year. Adequate supplemental calcium and vitamin D intake is important in women with osteoporosis if dietary intake is inadequate (see *"Warnings and special precautions").*

Treatment of osteoporosis in men:

For the treatment of osteoporosis in men, the recommended dose is a single intravenous infusion of 5 mg ACLASTA administered once a year.

Adequate supplemental calcium and vitamin D intake is important in men with osteoporosis if dietary intake is inadequate (See *"Warnings and special precautions").*

Treatment of glucocorticoid- induced osteoporosis:

For the treatment of glucocorticoid-induced osteoporosis, the recommended dose is a single intravenous infusion of 5 mg ACLASTA administered once a year.

Adequate supplemental calcium and vitamin D intake is important in patients with osteoporosis if dietary intake is inadequate (*"Warnings and special precautions").*

Treatment of Paget's disease of bone:

For the treatment of Paget's disease ACLASTA should be prescribed only by medical practitioners with experience in treatment of Paget's disease of the bone.

The recommended dose is one intravenous infusion of 5 mg ACLASTA (anhydrous) in 100 mℓ aqueous solution administered intravenously via a vented infusion line, given at a constant infusion rate.

Re-treatment of Paget's disease: Specific re-treatment data are not available.

After a single treatment with ACLASTA in Paget's disease, an extended remission period is observed in responding patients (see "*Pharmacodynamic properties*"). However, re-treatment with ACLASTA may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, in patients who failed to achieve normalisation of serum alkaline phosphatase, or in patients with symptoms, as dictated by medical Practice 12 months after the initial dose.

In patients with Paget's disease, 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 *"Warnings and special precautions").*

INSTRUCTIONS FOR USE AND HANDLING:

ACLASTA (5 mg in 100 mℓ ready to infuse solution) is administered intravenously via a vented infusion line, given at a constant infusion rate. The infusion time must not be less than 15 minutes.

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

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

Patients with renal impairment:

The use of ACLASTA in patients with creatinine clearance < 35 mℓ /min is not recommended due to limited clinical safety data in such patients. (See *"Warnings and special precautions"*).

No dose adjustment is necessary in patients with creatinine clearance ≥ 35 mℓ /min.

Patients with hepatic impairment:

No dose adjustment is required (see "*Pharmacokinetic properties*").

Children and adolescents:

ACLASTA is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

Elderly (≥ 65 years):

No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly patients and younger subjects.

SIDE EFFECTS:

ACLASTA has been most commonly associated with the following post-dose symptoms: fever (18.1 %), myalgia (9.4 %), flu-like symptoms (7.8 %), arthralgia (6.8 %) and headache (6.5 %), the majority of which occur within the first 3 days following ACLASTA administration. The majority of these symptoms were mild to moderate in nature and resolved within 3 days of the event onset. The incidence of these symptoms decreased markedly with subsequent doses of annual ACLASTA.

The incidence of post-dose symptoms occurring within the first 3 days after administration of ACLASTA can be reduced by approximately 50 % with the administration of paracetamol or ibuprofen shortly following ACLASTA administration as needed.

Table 1 lists the adverse reactions suspected (investigator assessment) to be associated with ACLASTA in the pooled studies supporting the indications: treatment of osteoporosis in men and postmenopausal women, prevention of clinical fractures after low trauma hip fracture, treatment and prevention of glucocorticoid- induced osteoporosis and Paget's disease of the bone by system organ class and by frequency using the following convention: very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥1/1 000, <1/100), rare (≥ 1/10 000, <1/1 000), very rare(< 1/10 000), including isolated cases.

Table 1: Adverse drug reactions suspected to be associated with ACLASTA treatment

Infections and infestations

Uncommon**:** Influenza, nasopharyngitis

Blood and lymphatic system disorders

Uncommon**:** Anaemia

Metabolism and nutrition disorders

Uncommon**:** Anorexia*, decreased appetite

Psychiatric disorders

Uncommon**:** Insomnia

Nervous system disorders

Common**:** Headache, dizziness

Uncommon**:** Lethargy*, paraesthesia, somnolence, tremor, syncope

Eye disorders

Uncommon: Conjunctivitis, eye pain

Rare: Uveitis*, episcleritis, iritis

Ear and labyrinth disorders

Uncommon: Vertigo

Vascular disorders

Uncommon: Hypertension, flushing

Respiratory, thoracic and mediastinal disorders

Uncommon: Cough, dyspnoea*

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhoea

Uncommon: Dyspepsia*, abdominal pain upper, abdominal pain*, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis*

Skin and subcutaneous tissue disorders

Uncommon:	Rash, hyperhidrosis*, pruritus, erythema
Musculoskeletal disorders	
Common:	Myalgia*, arthralgia*, bone pain, back pain, pain in extremity.
Uncommon:	Neck pain, musculoskeletal stiffness*, joint swelling*, muscle spasms, shoulder pain, musculoskeletal chest pain*, musculoskeletal pain, joint stiffness*, arthritis, muscular weakness
Renal and urinary disorders	
Uncommon:	Blood creatinine increased, pollakiuria, proteinuria
General disorders and administration site conditions	
Very common:	Fever
Common:	Flu-like symptoms, chills, fatigue*, asthenia, pain*, malaise,
Uncommon:	Peripheral oedema, thirst*, acute phase reaction*. non-cardiac chest pain

* Adverse reactions reported more frequently in the individual studies are:

Very common: myalgia, arthralgia, fatigue, pain.

Common: lethargy, dyspnoea, dyspepsia, oesophagitis, abdominal pain, hyperhidrosis, musculoskeletal (muscle) stiffness, joint swelling, musculoskeletal chest pain, joint stiffness, anorexia, thirst, acute phase reaction.

Uncommon: uveitis. Additional adverse reactions, which were reported in the individual studies but are not included in the Table 4-1 (due to a lower frequency in the Aclasta group compared with that of the placebo group when the data was pooled) include: ocular hyperaemia, C-reactive protein increased, hypocalcaemia, dysgeusia, toothache, gastritis, palpitation, infusion site reaction.

In one 3 year trial in postmenopausal women with osteoporosis (Horizon PFT), the overall incidence of all atrial fibrillation adverse events was 2.5 % (96 out of 3862) in the ACLASTA group vs. 1.9 % (75 out of 3852) in the placebo group.

The rate of atrial fibrillation serious adverse events was 1.3 % (51 out of 3,862) in patients receiving ACLASTA compared with 0.6 % (22 out of 3,852) patients receiving placebo. The mechanism behind the increased incidence of atrial fibrillation is unknown.

The imbalance observed in this trial has not been observed in other clinical trials with zoledronic acid. Most adverse events were of mild to moderate severity and did not lead to discontinuation.

Class effects:

Renal impairment:

Treatment with intravenous bisphosphonates, including ACLASTA, has been associated with renal impairment manifested as deterioration in renal function (i.e. increased serum creatinine) and in rare cases acute renal failure. Renal impairment has been observed following the administration of ACLASTA, especially in patients with pre-existing renal compromise or additional risk factors (e.g. oncology patients with chemotherapy, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, severe dehydration), the majority of who received a 4 mg dose every 3-4 weeks, but it has been observed in patients after a single administration.

In clinical trials, there were similar mild transient increases in serum creatinine levels in ACLASTA and placebo treated patients. In the studies to support the indications prevention of clinical fractures after hip fracture in postmenopausal women, treatment of osteoporosis in men, treatment of glucocorticoid-induced osteoporosis, the change in creatinine clearance (measured annually prior to dosing), and the incidence of renal failure and impairment was comparable for both the ACLASTA and placebo or comparator treatment groups.

Laboratory findings:

In the Paget's disease trials, symptomatic hypocalcaemia was observed in approximately 1 % of patients, all of which resolved. This was not seen in osteoporosis fracture prevention studies. In the HORIZON-RFT, treatment of male osteoporosis and treatment of glucocorticoid-induced osteoporosis trials, there were no patients who had treatment emergent serum calcium levels below 1.87 mmol/ℓ.

Local reactions:

This event rate was comparable for both the ACLASTA and placebo treatment groups. In the treatment of male osteoporosis trial, the event rate was 2.6 % in the zoledronic acid treatment group and 1.4 % in the alendronate treatment group. In the treatment of glucocorticoid-induced osteoporosis trial, no local reactions were reported.

Osteonecrosis of the jaw:

Cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with ACLASTA- (see "*Warnings and special precautions").*

In the HORIZON-PFT trial in 7736 patients, ONJ has been reported in one patient treated with ACLASTA and one patient treated with placebo. Both cases resolved. In the HORIZON-RFT, treatment of male osteoporosis and treatment of glucocorticoid- induced osteoporosis trials there were no cases of osteonecrosis of the jaw.

Adverse medicine reactions from post-marketing spontaneous reports:

The following adverse reactions have been reported during post approval use of zoledronic acid. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Hypersensitivity reactions including cases of bronchoconstriction, urticaria and angioedema, and cases of anaphylactic reaction/shock have been reported.

Cases of renal impairment including renal failure requiring dialysis, especially in patients with pre-existing renal compromise or other risk factors such as concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post infusion period have been reported.

The following events have been reported: dehydration secondary to post-dose symptoms such as fever, vomiting and diarrhoea; hypotension in patients with underlying risk factors; osteonecrosis of the jaw; scleritis and orbital inflammation.

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. Suspected adverse reactions can also be reported directly to the Holder of the Certificate of Registration (HCR) via the link: https://pvi1j.solutions.iqvia.com or the e-mail address: adverse.event.sac@sandoz.com.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Clinical experience with acute overdosage is limited. 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 infusion of calcium gluconate.

IDENTIFICATION:

The infusion is a clear and colourless aqueous solution.

PRESENTATION:

ACLASTA 5 mg/100 mℓ solution for infusion is supplied in a 100 mℓ transparent, colourless plastic vial 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 vial and multipacks comprising three or six packs, each containing one vial. Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS:

Store ACLASTA at or below 30 °C. Keep the original packaging unchanged and sealed until a doctor or a nurse administers ACLASTA. The ACLASTA bottle is for single use only. ACLASTA should be used immediately and the entire volume in the bottle should be administered.

The product does not contain preservatives. For microbiological reasons, the ready- to-use product should be used immediately after opening and the entire content should be administered. However, after opening the solution is chemically and physically stable for at least 24 hours at 2 to 8 °C.

REGISTRATION NUMBER:

A39/34/0575

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

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[1]Company Reg. No.: 1990/001979/07

Registered Trademark

Additional countries registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Aclasta 5mg/100ml infusion	NS2	08/34/0129
Botswana	Aclasta 5mg/100ml infusion	S2	BOT1101842

ATC code: A.34 Other

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