These Clinical Guidelines have been created using resources that were current as of the "Reviewed" date noted at the beginning of the document. Clinicians should refer to the manufacturer's Prescribing Information (or equivalent) for the most up-to-date information. While CarepathRx has published these Clinical Guidelines after a close review of available literature and a clinical review process, given the evolving nature and complexity of modern pharmaceutical products, CarepathRx does not and cannot warrant or guarantee that these Clinical Guidelines reflect the objectively best or highest standard of care at any given time.

Nothing within these Clinical Guidelines is intended to supersede or interfere with any individual clinician's decision-making or professional judgment with respect to either (1) prescribing or dispensing the drug or product in question or (2) the overall treatment plan for an individual patient.

Zoledronic Acid (Reclast, Zometa) Clinical Guideline for Home Intravenous Therapy

Policy ID: CG037
Effective: 8/7/2025
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Approved by, Title and Date Approved: Kathleen Patrick, President, 8/7/25

I. BACKGROUND

Zoledronic acid (Reclast, Zometa) is a bisphosphonate which inhibits bone resorption via action on osteoclasts and their precursors. Zoledronic acid inhibits osteoclastic activity and skeletal calcium release induced by tumors. Zoledronic acid decreases serum calcium and phosphorus and increases their elimination. In osteoporosis, osteoclast-mediated resorption is inhibited, reducing bone turnover. Zoledronic acid is indicated for the treatment of osteoporosis, bone metastases, hypercalcemia of malignancy, and Paget's disease. The following outlines the procedures for servicing patients in need of outpatient zoledronic acid infusions.

II. PATIENT ACCEPTANCE CRITERIA

A. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon the dispensing pharmacy's admission criteria.

B. The decision to administer a first dose in the home by a field nurse will be determined on a case-by-case basis and reviewed by nursing and pharmacy management. The following criteria will be evaluated:

1. Prescriber preference
2. Allergy profile
3. Age
4. Other relevant social and/or medical history

C. Physician orders for zoledronic acid must include:

1. Drug
2. Dose
3. Route of administration
4. Frequency of administration
5. Emergency medications per protocol
6. Orders for pre-medications
7. Line care protocol
8. Routine lab monitoring, if applicable

D. Baseline labs or tests prior to starting therapy:

1. Pregnancy status

2. Serum creatinine and fluid status
3. Bone mineral density at baseline
4. Serum calcium, phosphorus, magnesium, and vitamin D levels.

E. Dispensing pharmacy treatment protocol for anaphylaxis will be instituted for a first dose of zoledronic acid at home unless a more comprehensive patient-specific orders are provided by physician. See Appendix A (Nursing CarepathRx policy on *Management of Allergic/Anaphylactic Reactions*).

III. PHARMACOLOGY OVERVIEW

A. Indication and Dosing:

1. Bone metastases, solid tumor: 4 mg IV once every 3 to 4 weeks (Zometa)
2. Multiple myeloma: 4 mg IV once every 3 to 4 weeks (Zometa)
3. Hypercalcemia of malignancy: 4 mg IV as a single dose, may repeat after 7 days if hypercalcemia persists (Zometa)
4. Osteoporosis (Reclast)

    a. Treatment: 5 mg IV once every 12 months
    b. Prevention: 5 mg IV once every 2 years
    c. Glucocorticoid-induced: 5 mg IV every 12 months

5. Paget disease: 5 mg IV as a single dose, may consider repeat dose after 12 months (Reclast)

B. Dose Adjustments:

1. **Kidney dysfunction**:

    a. CrCl ≥ 35 mL/min: no dose adjustment, use with caution <80 mL/min
    b. CrCl < 35 mL/min or acute kidney impairment: contraindicated due to lack of safety and efficacy data

2. Indication Specific Recommendations (Upon treatment initiation):

a. For multiple myeloma and metastatic bone lesions from solid tumors, the recommended dose for patients with reduced renal function (mild to moderate renal impairment):

Baseline CrCl (mL/min)	Zoledronic Acid Recommended Dose*
greater than 60	4 mg
50 to 60	3.5 mg
40 to 49	3.3 mg
30 to 39	3 mg
KEY: *Doses calculated assuming target AUC of 0.66 (mg•hr/L) (CrCl=75 mL/min)	

b. Hypercalcemia of Malignancy:

i. SCr ≤4.5 mg/dL: No dosage adjustment necessary.
ii. SCr >4.5 mg/dL: Use not recommended unless benefit outweighs risk.

3. **Dose adjustment for renal toxicity:**

   a. Multiple Myeloma and metastatic bone lesions from solid tumors:

      i. Evaluate risk versus benefit. Treatment should be withheld for renal deterioration without apparent cause and may resume at the prior dose when renal function returns to within 10% of baseline.
      ii. Treatment should be withheld for unexplained albuminuria >500 mg per 24 hours until return to baseline, then reevaluate every 3 to 4 weeks; consider reinitiating with a longer infusion time of 30 minutes or longer.

   b. Hypercalcemia of malignancy: Evaluate risk versus benefit.

4. **Dialysis**: Use contraindicated for non-oncology indications and not recommended for oncology indications unless benefits outweigh risks due to lack of safety and efficacy data.

5. **Hepatic dose adjustments**: There are no dosage adjustments for hepatic dysfunction.

C. Duration:

6. Bone metastases, solid tumor: may continue indefinitely
7. Hypercalcemia of malignancy: Retreatment with Zometa 4 mg may be considered if serum calcium does not return to normal or remain normal after initial treatment; it is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose.
8. Multiple myeloma: continue for up to 2 years, then reassess risks and benefits; resume therapy upon relapse.
9. Osteoporosis: optimal duration unknown. Consider discontinuing after 3 years if bone mineral density is stable, there have been no previous fragility fractures, and short-term fracture risk is low. If fracture risk remains high, consider extending treatment for up to 6 years. Treatment may be resumed based on multiple factors such as decline in BMD, duration of discontinuation, and risk factors for fracture.
10. Paget Disease: A repeat 5 mg dose may be considered after 12 months in patients with biochemical relapse (i.e. increase in alkaline phosphatase), radiographic progression of disease, or recurrent pain.

D. Contraindications:

1. Anaphylaxis to zoledronic acid or any component of the formulation.
2. Hypocalcemia
3. CrCl < 35 mL/min or acute renal impairment.

E. Warnings and Precautions:

1. **Concomitant use**- Avoid using both Zometa and Reclast together.
2. **Hypocalcemia**- Hypocalcemia has been reported; patients with Paget disease may be at significant risk for hypocalcemia after treatment with zoledronic acid. Use with caution with other medications known to cause hypocalcemia and in patients with disturbances of calcium and mineral metabolism. Correct hypocalcemia before starting zoledronic acid therapy and closely monitor calcium levels.
3. **Renal impairment**- Single and multiple infusions in patients with both normal and impaired renal function have been associated with renal deterioration, resulting in renal failure and dialysis. Preexisting renal compromise, severe dehydration, and concurrent use with diuretics or other nephrotoxic drugs may increase the risk for renal impairment.

    a. Non-oncology Indications - Do not use single doses >5 mg. Patients with underlying moderate to severe renal impairment, increased age, concurrent use of nephrotoxic or diuretic medications, or severe dehydration prior to or after zoledronic acid administration may have an increased risk of acute renal impairment or renal failure. Correct dehydration prior to initiation.
    b. Oncology Indications - Use is not recommended in patients with serum creatinine >3 mg/dL and bone metastases (limited data). In patients with cancer, do not use single doses >4 mg. Risk factors for renal deterioration include preexisting renal insufficiency and repeated doses and other bisphosphonates therapy. Dehydration and the use of other nephrotoxic drugs which may contribute to renal deterioration should be identified and managed. Monitor serum creatinine before each dose.

4. **Osteonecrosis of the jaw**- Known risk factors include longer duration of use (3 years), invasive dental procedures, cancer diagnosis (particularly multiple myeloma), concomitant therapy including chemotherapy/corticosteroid/or angiogenesis inhibitors, poor oral hygiene, ill-fitting dentures, smoking, and comorbid conditions (including anemia, coagulopathy, infection, preexisting dental disease). Risk may increase with duration of use and may be reported based on tumor type. Invasive dental procedures should be avoided if possible, or initiation of therapy should be delayed until optimal dental health is attained. Preventive dental exams are recommended before starting zoledronic acid therapy.
5. **Bone fractures**- Atypic femur fractures, including subtrochanteric femur and diaphyseal femur fractures, have been reported, which may be preceded by prodromal pain weeks or months prior to fracture. Patients receiving IV therapy for >3 years may be at an increased risk. Patients with thigh or groin pain should be evaluated to rule out femoral fracture.
6. **Musculoskeletal pain**- Severe bone, joint, and/or muscle pain have been reported. Onset of pain ranged from one day to several months and resolves on discontinuation. Some patients experienced recurrence when rechallenged with the same drug or another bisphosphonate. Avoid use in patients with a history of these symptoms in association with bisphosphonate therapy.
7. **Dehydration**- Dehydration has occurred and may increase risk of renal deterioration. Withhold treatment until adequate hydration in patients with hypercalcemia of malignancy before administering; monitoring is recommended.
8. **Hypersensitivity reactions** including urticaria, angioedema, and anaphylactic reactions or shock.

9. **Bronchoconstriction:** Use with caution in patients with Aspirin-sensitive asthma as zoledronic acid may cause bronchoconstriction.
10. **Pregnancy and lactation**- Administration of zoledronic acid to pregnant rats during organogenesis resulted in fetal malformations and embryo-fetal lethality at maternal exposures that were greater than or equal to 2.4 times the human clinical exposure based on area under the curve (AUC). Zoledronic acid is incorporated into the bone matrix, from where it is gradually released over periods of weeks to years. There may be a risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during and after zoledronic acid treatment.

    It is not known whether zoledronic acid is present in human milk, or whether it affects milk production or the breastfed child. Zoledronic acid binds to bone long term and may be released over periods of weeks to years. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during and after zoledronic acid treatment.

    NIOSH Group 3- Non-antineoplastics with Reproductive Risks. This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk.

F. Pharmacokinetics:

1. Distribution: binds to bone
2. Protein binding: 23-53%
3. Metabolism: Metabolism not likely, primarily eliminated via the kidney intact.
4. Half-life elimination: 146 hours in terminal phase.
5. Excretion: Primarily urine within 24 hours, feces accounts for <3%.
6. AUC increases with renal function impairment.

G. Adverse Reactions:

1. Arthralgia (10%)
2. Peripheral edema (3-20%)
3. Abdominal pain (Up to 16%)
4. Constipation (6-27%)
5. Diarrhea (5-24%)
6. Nausea (4.5-46%)
7. Vomiting (2-32%)
8. Back pain (4.3-15%)
9. Pain in extremity (3.1-14%)
10. Headache (3.9-19%)
11. Nephrotoxicity (11-17%)
12. Fatigue (2.1-39%)
13. Influenza-like illness/acute phase reaction -A transient acute phase reaction including fever, chills, pain, myalgia, or other influenza-like symptoms may occur within 3 days of initial infusion, which typically resolves in 3-14 days.

H. Drug Interactions:

1. Increased effect/toxicity: Aminoglycosides, loop diuretics, angiogenesis inhibitors, calcitonin, deferasirox, NSAIDs.
2. Decreased effect: Proton pump inhibitors.
3. Drug-drug interactions may exist. Consult interaction database for patient specific assessment.

IV. ADMINISTRATIVE GUIDELINES

A. Administration: IV infusions should be given immediately after reconstitution and dilution. Begin infusion within 4 hours of preparation per current USP Immediate-Use Guidelines.

B. Do not co-administer with other products in the same IV line.

C. Hazardous handling: **It is the responsibility of the dispensing pharmacy to ensure medication handling is in compliance with organizational policies and procedures. This medication meets the definitions of a hazardous drug as outlined by the National Institute for Occupational Safety and Health (NIOSH).**

V. NURSING PROCEDURE

A. Supplies may include but are not limited to:

1. Alcohol Swabs
2. Gloves
3. Tape
4. IV access supplies as applicable:

    a. Peripheral IV access supplies for patients requiring peripheral IV access
        i. IV start Kit
        ii. Peripheral IV catheter (ex. 22 Gauge x1" and 24 Gauge x ¾")
        iii. Extension set 8" with needless connector

    b. Port access supplies for patients with a port
        i. Port needle (ex. 22 Gauge x ¾ to 1" safe step)
        ii. Needless connector
        iii. Central line dressing change kit

5. IV Pole
6. IV administration set (flow regulator or gravity tubing)
7. Syringes (10mL) and needles (20 G x 1")
8. Vented adapter spike (for ready to use glass bottles of zoledronic acid)
9. Chemo gloves
10. Chemo prep mat
11. Chemo spill kit and hazardous drug spill procedure
12. Protective gown

13. Trace/chemo disposable mail back container

B. Prescription items:

1. Drug: Vials of Zoledronic acid or ready-to-use infusion solution
2. 100 mL 0.9% sodium chloride diluent bag
3. 25 mL 0.9% sodium chloride stock bag for reduced doses utilizing RTU infusion solution
4. Standard flushes per protocol
5. Anaphylaxis kit (needed for first dosing)

C. How Supplied:

1. Reclast is supplied as 5 mg in a 100 mL ready to infusion solution in a glass bottle.
2. Zometa is provided as either:

    a. 4 mg per 100 mL solution in glass bottle or IV bag
    b. 4 mg/5 mL single-use vial of concentrate

D. Storage and Handling:

1. Reclast 4mg/5 mL vials and 4 mg/100mL ready to use solution - Store at room temperature, excursion from 15°C and 30°C (59°F to 86°F).
2. Zometa 4 mg/100mL ready to use solution- Store at room temperature, excursions from 15°C to 30°C (59°F-86°F).
3. Zometa 4mg/5 mL vials- Store at room temperature, excursion from o 15°C to 30°C (59°F-86°F).

E. Compatibility:

1. Zoledronic acid solution should not come in contact with calcium-containing or other divalent cation-containing infusion solutions such as Lactated Ringer's solution.
2. Zoledronic acid is stable in dextrose and 0.9% sodium chloride solutions.

F. Procedures:

1. Explain the reasoning for visit and use of zoledronic acid.
2. Ensure the patient is adequately hydrated prior to the infusion.
3. Don gloves and gown.
4. Establish venous access prior to preparation of drug.
5. Counsel patient on warnings, precautions, and potential side effects including but not limited to arthralgia, back pain, dehydration, bone fractures, renal dysfunction, and hypersensitivity reactions.
6. Don chemo gloves prior to preparation or spiking of the product.
7. Prepare the product:

    a. Reclast- 5mg/100mL ready to use solution. may be administered directly to the patient without further preparation. Use vented adapter spike to spike the glass bottle.

b. Zometa 4mg/100mL ready to use solution- This solution is ready-to-use and may be administered directly to the patient without further preparation. Use vented adapter spike to spike the glass bottle.
c. To prepare reduced doses for patients with baseline CrCl less than or equal to 60 mL/min, withdraw the specified volume of the Zometa from the container and replace with an equal volume of sterile 0.9% Sodium Chloride. Properly discard previously withdrawn volume of ready-to-use solution - do not store or reuse.

Table 2: Preparation of Reduced Doses–Zometa Ready-to-Use Bottle

Remove and discard the following Zometa ready-to-use solution (mL)	Replace with the following volume of sterile 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP (mL)	Dose (mg)
12.0	12.0	3.5
18.0	18.0	3.3
25.0	25.0	3.0

d. Zometa 4mg vials:
   i. Withdraw 4mg/5mL and add to 100mL 0.9% NaCl bag.
   ii. To prepare reduced doses for patients with baseline CrCl less than or equal to 60 mL/min, withdraw the specified volume of the Zometa concentrate from the vial for the dose required and add to 100mL 0.9% NaCl bag.

Table 3: Preparation of Reduced Doses–Zometa Concentrate

Remove and Use Zometa Volume (mL)	Dose (mg)
4.4	3.5
4.1	3.3
3.8	3.0

8. Infusion rates: Infuse over at least 15 minutes for all indications. If treatment is withheld for unexplained albuminuria, consider increasing the infusion time to at least 30 minutes upon reinitiation.
9. Discard waste in chemotherapy/trace disposable container.
10. Post infusion monitoring: Monitor patient and vital signs periodically during the infusion and 30 minutes after the infusion is complete per CarePathRx Nursing Best Practice Administration Guidelines.

VI. CLINICAL MONITORING

A. Prior to initiation:

1. Dental exam and preventative dentistry for patients at risk for osteonecrosis (i.e. cancer patients) performed by the patient's oral care clinician.
2. Pregnancy status
3. Serum creatinine and fluid status
4. Bone mineral density at baseline
5. Serum calcium, phosphorus, magnesium, and vitamin D level

B. During therapy:

1. Monitor for signs/symptoms of atypical femur fractures, musculoskeletal pain, and signs of ocular inflammation.
2. Monitor serum creatinine prior to each dose, evaluate fluid status and adequately hydrate patients prior to and following administration.
3. In osteoporosis: Serial bone mineral density (BMD) should be evaluated at baseline and every 1 to 3 years on treatment serum calcium and 25(OH)D.
4. Annual measurements of height and weight
5. Assessment of chronic back pain
6. Laboratory work including calcium, vitamin D, phosphorus, and magnesium.
7. Paget's disease: Serum total alkaline phosphatase at 6 to 12 weeks for initial response to treatment and potentially at 6 months; following treatment completion, monitor at ~1- to 2-year intervals.
8. Monitor during and for an appropriate time after administration for hypersensitivity and/or infusion reactions.

Please refer to the package insert for the most up to date guidance on this medication.

REFERENCES

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APPENDIX A: ANAPHYLAXIS KIT INTRUCTIONS

Emergency Medication After Your Infusion

Please call your pharmacy if you have any questions or concerns. In the event of an emergency, always call 911.

Your nurse will tell you when you need to use Emergency Medications.
The epinephrine dose will be noted on the Anaphylaxis Protocol included with your kit.

Start with a clean work surface and clean hands.

Open the supply bag labeled Anaphylaxis Kit Contents.

You will need:

1. **Bag containing Pills** (2 Acetaminophen and 2 Diphenhydramine)
2. **Bag containing Alcohol Prep Pads**
3. **Bag labeled IM Epinephrine**

All other contents will not be needed.

Open the IM Epinephrine Bag

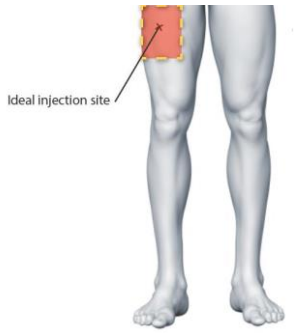
1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampule use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampule of epinephrine

Prepare IM (intramuscular) injection of Epinephrine:

1. **Attach the brown filtered needle to syringe**
    a. Be careful to not touch the tip of the syringe or the needle.
2. Using an **alcohol swab, wipe the neck of the epinephrine ampule.**
3. Holding the ampule upright, **swirl and flick the ampule until all fluid flows to the bottom chamber** (the top chamber should be empty).
4. Using a new alcohol wipe, grasp the neck of the ampule and with your other hand grasp the bottom chamber of the ampule. **Quickly snap the top of the ampule off, directing the snap way from you.**

5. **Place the tip of the brown filter needle inside the ampule**. Tilting the ampule, **withdraw dose of medication into the syringe** by gently pulling back on the plunger. Be careful to not pull the plunger out of the syringe.
6. Remove the needle from the ampule and h**old the syringe upright** with the needle pointing upward. **Gently tap the side of the syringe to bring any air to the top of the syringe.**
7. **Push the air out of the syringe by gently pushing on the plunger**.
8. Replace the cap on the brown filter needle. Discard remainder in ampule.
9. **Remove the brown filter needle and place the black safety needle onto the syringe.**

Give your IM Epinephrine injection



1. **Grasp your leg muscle at the outer mid-thigh** and **cleanse the area** with a new alcohol wipe.
2. **Push the needle into your leg muscle straight** in at a 90-degree angle.
3. **Inject the medication** by depressing the plunger in a slow and steady motion.
4. **Remove the needle** and wipe the site with the alcohol wipe.
5. May repeat dose every 5 minutes (**maximum 3 doses**) if ordered per protocol.

Take the pills by mouth.

a. 2 – Acetaminophen
b. 2 – Diphenhydramine

Place all trash in the bag the pills came in and take with you when you seek medical care. **Give the bag to the nurse or EMT**, so your doctor will know what medication you already took. They will properly dispose of the syringe and needles.
Call 911 or have someone drive you to the emergency department.

APPENDIX B: EPINEPRINE KIT INSTRUCTIONS FOR IM INJECTION

<u>Emergency Medication After Your Infusion</u>

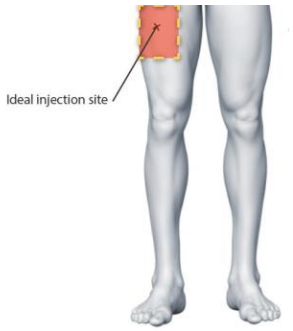
Please call 1-800-755-4704 if you have any questions or concerns. We are available 24 hours a day, 7 days a week. In the event of an emergency, always call 911.
Your nurse will tell you when you need to use Emergency Medications.
Start with a clean work surface and clean hands.
Open the supply bag labeled <u>Epinephrine Kit Contents</u>.

1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampule of epinephrine

Prepare IM (intramuscular) injection of Epinephrine:

2. **Attach the brown filtered needle to syringe**
    a. Be careful to not touch the tip of the syringe or the needle.
3. Using an **alcohol swab, wipe the neck of the epinephrine ampule**
4. Holding the ampule upright, **swirl and flick the ampule until all fluid flows to the bottom chamber** (the top chamber should be empty).
5. Using a new alcohol wipe, grasp the neck of the ampule and with your other hand grasp the bottom chamber of the ampule. **Quickly snap the top of the ampule off, directing the snap way from you.**
6. **Place the tip of the brown filter needle inside the ampule**. Tilting the ampule, **withdrawal all the medication into the syringe** by gently pulling back on the plunger. Be careful to not pull the plunger out of the syringe.
7. Remove the needle from the ampule and h**old the syringe upright** with the needle pointing upward. **Gently tap the side of the syringe to bring any air to the top of the syringe.**
8. **Push the air out of the syringe by gently pushing on the plunger**.
9. Replace the cap on the brown filter needle.
10. **Remove the brown filter needle and place the black safety needle onto the syringe.**

Give your IM Epinephrine injection



2. **Grasp your leg muscle at the outer mid-thigh** and **cleanse the area** with a new alcohol wipe.
3. **Push the needle into your leg muscle straight** in at a 90-degree angle.
4. **Inject the medication** by depressing the plunger in a slow and steady motion.
5. **Remove the needle** and wipe the site with the alcohol wipe.

Place all trash in the bag and take with you when you seek medical care. **Give the bag to the nurse or EMT**, so your doctor will know what medication you already took. They will properly dispose of the syringe and needles.

Call 911 or have someone drive you to the emergency department.