

Bisphosphonates and bone agents

Oral and IV bisphosphonates slow bone breakdown by driving osteoclasts to apoptosis, and this page places them alongside two mechanistically distinct bone drugs often taught in the same breath - denosumab, an antibody that blocks a different resorption signal and carries its own rebound-fracture risk on stopping, and teriparatide/abaloparatide, anabolic PTH-pathway analogs that build bone rather than merely slow its loss.

Online guide: <https://www.medguideglobal.com/pharmacology/endocrine-and-metabolic/bisphosphonates-and-bone-agents>
Content updated: 2026-09-15

Quick revision

One Liner: Nitrogen-containing bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid) stop osteoclasts from resorbing bone by blocking an enzyme in the same pathway statins act on; denosumab blocks a different resorption signal entirely; teriparatide and abaloparatide are the odd ones out - they build new bone rather than just slowing its loss.

1. Nitrogen-containing bisphosphonates inhibit farnesyl pyrophosphate synthase in the mevalonate pathway inside osteoclasts, which impairs the cytoskeletal attachment osteoclasts need to resorb bone and drives them to apoptosis. [6]
2. Oral bisphosphonates must be taken on an empty stomach with plain water, at least 30 minutes before the first food, beverage or other medication of the day, with the patient remaining upright and not lying down for at least 30 minutes, because of poor intrinsic absorption and a real esophageal irritation risk. [1]
3. Osteonecrosis of the jaw and atypical, low-trauma femoral shaft fractures are labelled risks of bisphosphonates as a class, more often reported with the higher cumulative exposure typical of IV oncologic dosing but described for oral use in osteoporosis as well. [1][2]
4. Zoledronic acid (Reclast) is a once-yearly IV infusion contraindicated in patients with creatinine clearance below 35 mL/min, and it commonly causes an acute-phase reaction - fever, myalgia, flu-like symptoms - in the days after the first infusion. [2]
5. Denosumab is not a bisphosphonate: it is a monoclonal antibody that binds RANKL, the signal osteoclasts need to form, function and survive, and blocking it suppresses resorption by an entirely separate mechanism. [3]
6. Stopping denosumab causes a rebound rise in bone turnover and an increased risk of vertebral fracture, including multiple vertebral fractures, which is why its label calls for transitioning to another antiresorptive rather than simply discontinuing it. [3]
7. Teriparatide and abaloparatide are parathyroid hormone-pathway analogs - teriparatide is PTH(1-34) itself, abaloparatide is a PTHrP(1-34) analog - and both are anabolic, stimulating new bone formation rather than only slowing resorption. [4][5]
8. Both PTH-pathway analogs caused a dose-dependent increase in osteosarcoma in rats at high, prolonged exposures, which is why both labels restrict lifetime use to no more than two years and advise avoiding them in patients with other osteosarcoma risk factors. [4][5]

Overview

1. Bone is not a static scaffold: osteoclasts continuously resorb old bone and osteoblasts lay down new bone in a coupled remodelling cycle. Osteoporosis develops when resorption outpaces formation, and the two oldest strategies for treating it target opposite sides of that cycle - slow the resorption side down, or push the formation side up. Bisphosphonates, and denosumab alongside them, belong to the first strategy; teriparatide and abaloparatide belong to the second. This page groups all of them under "bone agents" because a clinician choosing among them is making

exactly that antiresorptive-versus-anabolic decision, even though only the bisphosphonates share a single chemical mechanism. [6]

2. Within the bisphosphonates, nitrogen-containing members - alendronate, risedronate, ibandronate and zoledronic acid - are the ones in routine osteoporosis use today. They work by inhibiting farnesyl pyrophosphate synthase, an enzyme in the mevalonate pathway, inside osteoclasts. Losing that enzyme's product impairs the prenylation of small GTPases the osteoclast's cytoskeleton depends on to attach to bone, and the cell undergoes apoptosis instead of completing a resorption cycle. This is a genuinely different chemistry from the older non-nitrogen-containing bisphosphonates (etidronate, clodronate), which are instead metabolised into a toxic ATP analog - a pathway with a narrower safety margin against impairing bone mineralisation itself, which is part of why the nitrogen-containing members dominate current practice. [6]

3. Two long-term risks recur across every nitrogen-containing bisphosphonate label and are the ones most worth knowing cold: osteonecrosis of the jaw (ONJ), an area of exposed, non-healing jawbone usually precipitated by a dental extraction or local infection, and atypical femoral fracture (AFF), a low-trauma fracture of the femoral shaft that behaves differently from an osteoporotic fragility fracture and is often preceded by prodromal thigh or groin pain. Both are described in the alendronate and zoledronic acid labels as reported with bisphosphonate use generally, with higher absolute risk at the higher cumulative doses used in oncology than at osteoporosis doses. [1][2]

4. Denosumab is grouped on this page as a bone agent rather than a bisphosphonate because it is not one, mechanistically or chemically - it is a fully human monoclonal antibody against RANKL, the ligand osteoclast precursors need to differentiate into mature, resorbing osteoclasts. Blocking RANKL suppresses resorption from a different point in the pathway than a bisphosphonate does, and unlike a bisphosphonate, denosumab's effect is not stored in bone once dosing stops - turnover rebounds, which the label ties to an increased risk of vertebral fracture, including multiple vertebral fractures, after discontinuation. [3]

5. Teriparatide and abaloparatide sit furthest from the bisphosphonates mechanistically. Both act through the PTH type 1 receptor - teriparatide is recombinant human PTH(1-34) itself, abaloparatide is a synthetic analog of PTH-related protein, PTHrP(1-34) - and, given intermittently, that signalling stimulates new bone formation on trabecular and cortical surfaces rather than simply slowing resorption. Both labels report the same rat carcinogenicity finding - a dose- and duration-dependent rise in osteosarcoma at exposures well above the human therapeutic dose - and both restrict lifetime treatment to no more than two years as a result, even though it remains unknown whether the finding translates to humans at labelled doses. [4][5]

Classification and drug examples

Intro: Three genuinely different mechanisms are taught together here because they are prescribed as alternatives to one another for the same clinical problem. Only the first group is chemically "bisphosphonates"; the other two are contrast agents included for the comparison a clinician actually has to make.

1. Name: Oral nitrogen-containing bisphosphonates

1. Note: First-line antiresorptive agents for most patients; effectiveness depends heavily on correct fasting-state administration because oral bioavailability is inherently very low.

1. Name: Alendronate

Fosamax

1. Route: Oral, daily or weekly

1. Note: The most widely used oral bisphosphonate; must be taken on an empty stomach, at least 30 minutes before food, other medication or another beverage, with the patient remaining upright afterward. [1]

2. Name: Risedronate

Actonel

2. Route: Oral, daily, weekly or monthly

2. Note: Comparable oral dosing-instruction requirements to alendronate. [6]

3. Name: Ibandronate

Boniva

3. Route: Oral monthly, or IV quarterly

3. Note: The only member of this group with both an oral and an IV formulation in routine use; not found in this site's medicine registry as an individually reviewed page at the time of writing. [6] [1]

2. Name: IV bisphosphonate

2. Note: Bypasses the very low oral bioavailability and the esophageal irritation risk entirely, at the cost of an acute-phase reaction after the first infusion and a stricter renal cut-off.

Name: Zoledronic acid

1. Reclast

2. Zometa

Route: IV infusion, once yearly for osteoporosis

Note: Contraindicated at creatinine clearance below 35 mL/min; commonly causes fever, myalgia and flu-like symptoms within the first three days after infusion. [2] [2]

3. Name: RANKL inhibitor (not a bisphosphonate)

3. Note: Included here as a bone agent, not as a bisphosphonate - the mechanism, dosing route and discontinuation risk are all genuinely different.

Name: Denosumab

1. Prolia

2. Xgeva

Route: Subcutaneous injection, twice yearly (Prolia) or monthly (Xgeva, oncology dosing)

Note: Binds RANKL to block osteoclast formation and survival; stopping it causes rebound bone turnover and an increased risk of vertebral fracture, so the label calls for transitioning to another antiresorptive rather than simple discontinuation. [3] [3]

4. Name: PTH-pathway anabolic agents (not bisphosphonates)

4. Note: The only anabolic option on this page - they build new bone rather than only slowing its breakdown - and the only ones carrying the rat osteosarcoma finding and its two-year lifetime-use limit.

1. Name: Teriparatide

Forteo

1. Route: Subcutaneous injection, daily

1. Note: Recombinant human PTH(1-34); dose-dependent osteosarcoma incidence in rats led to a two-year lifetime-use limit. [4]

2. Name: Abaloparatide

Tymlos

2. Route: Subcutaneous injection, daily

2. Note: A PTHrP(1-34) analog acting at the same PTH1 receptor; carries the same rat osteosarcoma finding and the same two-year lifetime-use limit as teriparatide. [5] [4][5]

Mechanism of action

Summary: Nitrogen-containing bisphosphonates bind avidly to hydroxyapatite at sites of active bone remodelling and are taken up by osteoclasts during resorption. Inside the osteoclast they inhibit farnesyl pyrophosphate synthase in the mevalonate pathway - the same biochemical pathway statins inhibit in the liver - which prevents prenylation of small GTPases the osteoclast's cytoskeleton needs to maintain its ruffled border and attach to bone. The osteoclast can no longer resorb bone effectively and undergoes apoptosis, which is why the bisphosphonate mechanism is antiresorptive rather than anabolic: it removes resorbing cells rather than adding bone-forming ones.

Target: Farnesyl pyrophosphate synthase inside osteoclasts (bisphosphonates); RANKL, the osteoclast-differentiation ligand (denosumab); the PTH type 1 receptor on osteoblasts (teriparatide, abaloparatide)

Cidal Static: Antiresorptive via osteoclast apoptosis (bisphosphonates) or osteoclast-formation blockade (denosumab);

anabolic via new bone formation (teriparatide, abaloparatide) - none of these terms is literally cytotoxic/cytostatic in the anti-infective sense, but the antiresorptive-versus-anabolic distinction plays the same organising role for this class

Kill Kinetics: Bisphosphonates bind bone mineral for years and their effect persists long after the last dose because the drug is released slowly as bone remodels; denosumab's effect requires continued dosing and reverses within months of stopping; teriparatide and abaloparatide's anabolic effect also requires continued intermittent dosing and is typically followed by an antiresorptive agent to preserve the gained bone

1. Step: 1

1. Title: The bisphosphonate binds hydroxyapatite at an active bone-remodelling site

1. Detail: Because bisphosphonates have high affinity for bone mineral, they concentrate specifically where osteoclasts are actively resorbing rather than distributing evenly through bone. [6]

2. Step: 2

2. Title: An osteoclast internalises the drug while resorbing that bone surface

2. Detail: The osteoclast takes up the bisphosphonate as part of its normal resorptive activity, delivering the drug inside the very cell it will inactivate. [6]

3. Step: 3

3. Title: Nitrogen-containing bisphosphonates inhibit farnesyl pyrophosphate synthase

3. Detail: This blocks the mevalonate pathway step needed to prenylate small GTPases (Rho, Rac, Rab) that the osteoclast's cytoskeleton and ruffled border depend on. [6]

4. Step: 4

4. Title: Loss of prenylation disables the osteoclast's ability to resorb bone and triggers apoptosis

4. Detail: The osteoclast detaches from the bone surface and dies rather than completing a resorption cycle, reducing the number of active resorbing cells. [6]

5. Step: 5

5. Title: In parallel, denosumab and the PTH-pathway analogs act on different cells entirely

5. Detail: Denosumab binds circulating and bone-surface RANKL before it can engage its receptor RANK on osteoclast precursors, preventing those precursors from ever maturing into resorbing osteoclasts. Teriparatide and abaloparatide instead activate the PTH1 receptor on osteoblasts, and intermittent (rather than continuous) receptor activation favours bone formation over resorption, the opposite direction from the other two mechanisms on this page. [3][4]

Major clinical uses

1. Drug: Alendronate, risedronate

1. Organism: Not applicable

1. Indication: Treatment and prevention of postmenopausal osteoporosis; osteoporosis in men; glucocorticoid-induced osteoporosis; Paget's disease of bone

1. Line: first-line antiresorptive for most patients able to tolerate oral dosing instructions

1. Note: Requires normal renal function and the ability to remain upright for at least 30 minutes after dosing; not appropriate for patients with significant esophageal disease. [1]

2. Drug: Zoledronic acid

2. Organism: Not applicable

2. Indication: Postmenopausal osteoporosis; osteoporosis in men; prevention and treatment of glucocorticoid-induced osteoporosis; Paget's disease of bone

2. Line: alternative when oral dosing cannot be followed, or when adherence to a daily/weekly oral regimen is a concern

2. Note: Once-yearly IV dosing avoids the esophageal and adherence issues of oral bisphosphonates but requires adequate renal function and hydration before infusion. [2]

3. Drug: Denosumab

3. Organism: Not applicable

3. Indication: Osteoporosis in postmenopausal women and men at high fracture risk; bone loss from hormone-ablation therapy in certain cancers (at the Prolia dose); prevention of skeletal-related events in bone metastases (at the higher Xgeva dose)
3. Line: option for patients with renal impairment where bisphosphonates are avoided, or after bisphosphonate failure
3. Note: Requires a plan for what antiresorptive follows it, because stopping denosumab causes rebound bone turnover. [3]
4. Drug: Teriparatide, abaloparatide
4. Organism: Not applicable
4. Indication: Severe osteoporosis with high fracture risk, including glucocorticoid-induced osteoporosis, where an anabolic approach is preferred to an antiresorptive one
4. Line: reserved for high or very-high fracture-risk patients per current guideline recommendations, often followed by an antiresorptive agent to consolidate the gained bone
4. Note: Limited to a maximum of two years of lifetime use because of the rat osteosarcoma finding; avoided in patients with other osteosarcoma risk factors such as Paget's disease or prior skeletal radiation. [4][5][7]

Pharmacokinetics

1. Drug: Alendronate
1. Route: Oral, daily or weekly
1. Absorption: Very poor oral bioavailability (roughly 0.6-0.7% under fasting conditions), reduced further by any food, beverage other than plain water, or concomitant medication
1. Csf Penetration: Not applicable
1. Metabolism: Not metabolised
1. Elimination: Renal; a fraction binds to bone and is retained for years, released gradually during subsequent bone remodelling
1. Dose Adjust: Not recommended when creatinine clearance is below 35 mL/min [1]
2. Drug: Zoledronic acid
2. Route: IV infusion
2. Absorption: Not applicable (given intravenously)
2. Csf Penetration: Not applicable
2. Metabolism: Not metabolised
2. Elimination: Renal; bone-bound fraction released slowly over subsequent remodelling
2. Dose Adjust: Contraindicated at creatinine clearance below 35 mL/min or with evidence of acute renal impairment [2]
3. Drug: Denosumab
3. Route: Subcutaneous injection
3. Absorption: Well absorbed subcutaneously as a monoclonal antibody
3. Csf Penetration: Not applicable
3. Metabolism: Degraded via normal immunoglobulin catabolic pathways rather than hepatic or renal clearance mechanisms
3. Elimination: Not primarily renal, unlike the bisphosphonates
3. Dose Adjust: Correct pre-existing hypocalcemia before starting; monitor calcium especially in advanced chronic kidney disease [3]
4. Drug: Teriparatide, abaloparatide
4. Route: Subcutaneous injection, daily
4. Absorption: Well absorbed subcutaneously
4. Csf Penetration: Not applicable
4. Metabolism: Peptide hormones cleared by nonspecific proteolysis rather than a single organ-dependent pathway

4. Elimination: Not primarily renal in the way the bisphosphonates are

4. Dose Adjust: Lifetime treatment duration capped at two years for both drugs regardless of renal or hepatic status [4][5]

1. This page gives no dose regimens by design. Which bisphosphonate, which route, and for how long is a decision for the treating clinician working from a current prescribing reference and the patient's renal function, GI tolerance and fracture-risk category.

2. The oral bisphosphonates' single most clinically important pharmacokinetic fact is not a number but an instruction: bioavailability is so low, and so sensitive to co-ingested food or liquid, that the fasting-state dosing rule is not a minor convenience - skipping it can mean the dose is not meaningfully absorbed at all. [1]

3. Bisphosphonates bound to bone are released gradually over years as bone remodels, which is why their antifracture effect persists well after the last dose and why "drug holidays" are a real, guideline-discussed option for low-risk patients after several years of therapy - unlike denosumab, whose effect reverses within months of stopping. [2][3]

Adverse effects

1. Effect: Esophageal irritation

1. Detail: Esophagitis, esophageal ulcers and esophageal erosions are described with oral bisphosphonates, which is the rationale behind the strict upright, empty-stomach dosing instructions. [1]

2. Effect: Acute-phase reaction after IV infusion

2. Detail: Fever, myalgia, flu-like symptoms and headache occur in a meaningful proportion of patients in the days after a first zoledronic acid infusion, typically less pronounced with subsequent infusions. [2]

3. Effect: Hypocalcemia

3. Detail: Denosumab can cause hypocalcemia, which the label states must be corrected before starting treatment, with the risk markedly higher in advanced chronic kidney disease. [3]

4. Effect: Injection-site reactions and hypercalcemia

4. Detail: Teriparatide and abaloparatide, as daily subcutaneous injections that transiently raise PTH-pathway signalling, are associated with injection-site symptoms and transient increases in serum calcium. [4]

1. Effect: Osteonecrosis of the jaw (ONJ)

1. Detail: Described across the bisphosphonate class and for denosumab, generally associated with a dental extraction or local infection and delayed healing; it can also occur spontaneously.

1. Action: A dental assessment before starting long-term bisphosphonate or denosumab therapy, and avoiding invasive dental work during treatment where possible, is standard practice; new jaw pain, swelling or exposed bone during treatment is evaluated promptly. [1][2][3]

2. Effect: Atypical femoral fracture (AFF)

2. Detail: A low-energy, low-trauma fracture of the femoral shaft, often preceded by weeks to months of prodromal thigh or groin pain, reported across the bisphosphonate class and with denosumab.

2. Action: New thigh or groin pain during long-term antiresorptive therapy is a reason to evaluate for an incomplete femoral fracture rather than assume routine musculoskeletal pain. [1][2][3]

3. Effect: Severe hypocalcemia

3. Detail: Denosumab can cause severe, symptomatic hypocalcemia, including fatal cases, with substantially higher risk in patients with advanced chronic kidney disease or chronic kidney disease-mineral bone disorder.

3. Action: Pre-existing hypocalcemia is corrected before the first dose, and calcium is monitored, particularly in renal impairment. [3]

4. Effect: Rebound vertebral fracture after denosumab discontinuation

4. Detail: Stopping denosumab is followed by a rebound increase in bone turnover and an increased risk of vertebral fracture, including multiple vertebral fractures occurring close together.

4. Action: The label directs transitioning to an alternative antiresorptive agent rather than simply stopping denosumab without a follow-on plan. [3]

5. Effect: Osteosarcoma (animal finding)

5. Detail: Both teriparatide and abaloparatide caused a dose- and duration-dependent increase in osteosarcoma incidence in rats at exposures well above the human clinical dose; it is not known whether this translates to humans at labelled doses.

5. Action: Both drugs are avoided in patients with other osteosarcoma risk factors (Paget's disease, unexplained elevated alkaline phosphatase, open epiphyses, prior skeletal radiation, bone metastases or a history of skeletal malignancy), and lifetime use is capped at two years. [4][5]

6. Effect: Renal impairment (bisphosphonates)

6. Detail: Zoledronic acid is contraindicated below a creatinine clearance of 35 mL/min, and acute renal failure has been reported, particularly with rapid infusion or in patients with pre-existing renal disease or dehydration.

6. Action: Renal function is checked before each IV dose and hydration status assessed beforehand. [2]

1. Drug: Alendronate

1. Effect: The clearest labelled illustration of the fasting-dose rule: taking it with food, another beverage, or lying down afterward meaningfully reduces both absorption and safety margin against esophageal irritation. [1]

2. Drug: Zoledronic acid

2. Effect: Uniquely among the drugs on this page requires a specific pre-infusion renal and hydration check each time it is given, because it is dosed as a bolus IV exposure rather than daily oral titration. [2]

3. Drug: Denosumab

3. Effect: The only drug on this page whose stopping, not its starting, carries a distinct labelled fracture-risk warning. [3]

4. Drug: Teriparatide, abaloparatide

4. Effect: The only drugs on this page with a labelled lifetime duration cap tied to a carcinogenicity signal rather than to a renal or infusion-related risk. [4][5]

Contraindications, precautions and interactions

1. Zoledronic acid: creatinine clearance below 35 mL/min, or evidence of acute renal impairment. [2]

2. Known hypersensitivity to the specific drug is an absolute contraindication across all four agents. [1][2][3][4]

1. Uncorrected hypocalcemia must be treated before starting denosumab. [3]

2. Significant esophageal abnormalities that delay esophageal emptying (stricture, achalasia) are a caution for oral bisphosphonates because of the esophagitis risk. [1]

3. Paget's disease of bone, unexplained elevations of alkaline phosphatase, open epiphyses, prior external-beam or implant radiation involving the skeleton, bone metastases, or a hereditary disorder predisposing to osteosarcoma are reasons to avoid teriparatide and abaloparatide given their osteosarcoma signal. [4][5]

4. An upcoming invasive dental procedure is a reason to discuss timing carefully with both the dentist and the prescriber before starting or continuing a bisphosphonate or denosumab, given the ONJ association. [1][3]

1. With: Calcium, iron, magnesium or aluminium-containing products, and other oral medications taken close to the bisphosphonate dose

1. Effect: Meaningfully reduce oral bisphosphonate absorption, which is why the fasting window before other intake is part of the dosing instruction rather than a general suggestion. [1]

2. With: Aspirin and NSAIDs

2. Effect: May add to the gastrointestinal irritation risk of oral bisphosphonates. [1]

3. With: Other bone-active agents

3. Effect: Combining an antiresorptive with an anabolic agent, or switching between them, is a sequencing decision made by the treating clinician rather than a routine co-prescription. [7]

Comparison tables

Title: Antiresorptive or anabolic - and what stopping it costs you

Caption: Four mechanisms, one clinical problem. The distinguishing question for exam purposes is usually mechanism

(resorption vs formation) and what happens when the drug is stopped.

1. Key: agent

1. Label: Agent

1. Is Row Header: true

2. Key: mechanism

2. Label: Mechanism

3. Key: direction

3. Label: Antiresorptive or anabolic

4. Key: stopping

4. Label: Effect of stopping

1. Agent: Alendronate / risedronate / zoledronic acid

1. Mechanism: Inhibit farnesyl pyrophosphate synthase, driving osteoclast apoptosis

1. Direction: Antiresorptive

1. Stopping: Effect persists for years, released gradually as bone-bound drug is remobilised during remodelling [6]

2. Agent: Denosumab

2. Mechanism: Monoclonal antibody against RANKL, blocking osteoclast formation and survival

2. Direction: Antiresorptive

2. Stopping: Rebound increase in bone turnover and vertebral fracture risk within months; label directs transitioning to another antiresorptive [3]

3. Agent: Teriparatide / abaloparatide

3. Mechanism: PTH1 receptor agonism (PTH(1-34) or PTHrP(1-34) analog) via intermittent dosing

3. Direction: Anabolic

3. Stopping: Anabolic effect requires continued dosing; commonly followed by an antiresorptive agent to consolidate gained bone [4]

High-yield exam pearls

1. Pearl: "Nitrogen-containing" bisphosphonates block farnesyl pyrophosphate synthase; non-nitrogen-containing ones are metabolised into a toxic ATP analog instead.

1. Why: It is the mechanistic line examiners draw between the modern agents (alendronate, risedronate, zoledronic acid) and the older, now rarely used ones (etidronate, clodronate). [6]

2. Pearl: The oral bisphosphonate dosing rule - empty stomach, plain water, upright for 30 minutes - is not a compliance nicety; bioavailability is under 1% and drops further with any co-ingested food or drink.

2. Why: It explains why a patient who takes alendronate with breakfast may be getting essentially no drug effect at all, independent of any side effect. [1]

3. Pearl: ONJ and atypical femoral fracture are both bisphosphonate-class risks, but they are opposite ends of the same drug's action: prolonged suppression of bone turnover can both starve the jaw of the remodelling it needs to heal after dental trauma and let microdamage accumulate unrepaired in the femoral shaft.

3. Why: Understanding the shared mechanistic root - over-suppressed remodelling - explains why both risks rise with cumulative bisphosphonate exposure rather than being unrelated side effects. [1][2]

4. Pearl: Denosumab is the one bone agent on this page where stopping the drug, not starting it, has its own labelled warning.

4. Why: Because denosumab is not stored in bone the way a bisphosphonate is, its antiresorptive effect reverses on a timescale of months, producing a rebound fracture risk that has no bisphosphonate equivalent. [3]

5. Pearl: Teriparatide and abaloparatide are the only anabolic agents here, and the only two with a rat osteosarcoma signal and a two-year lifetime cap.

5. Why: It is the single fact that most reliably distinguishes this subclass from every antiresorptive agent on the page in an exam question. [4][5]

Common exam traps

1. Trap: Calling denosumab a bisphosphonate because it is used for the same indication.
1. Correction: Denosumab is a RANKL-targeting monoclonal antibody with a distinct mechanism, dosing route and discontinuation risk profile from any bisphosphonate. [3]
2. Trap: Assuming any antiresorptive agent can simply be stopped once bone density improves, the way a course of antibiotics ends.
2. Correction: Bisphosphonates leave residual bone-bound drug that keeps working for years, but denosumab does not - stopping it without a follow-on antiresorptive is specifically associated with rebound vertebral fracture. [3]
3. Trap: Treating teriparatide and abaloparatide as interchangeable with bisphosphonates in mechanism because both are used for osteoporosis.
3. Correction: They are anabolic PTH-pathway agonists that build new bone, mechanistically opposite to the antiresorptive bisphosphonates and denosumab, and they carry a distinct carcinogenicity-based lifetime dosing limit that the antiresorptive agents do not share. [4]
4. Trap: Assuming the oral bisphosphonate dosing instructions are about tolerability alone.
4. Correction: They exist primarily because oral bioavailability is extremely low and highly sensitive to co-ingested food, beverage or medication - skipping the instructions can mean inadequate drug exposure, not just a higher side-effect risk. [1]

Self-test questions

1. Question: What is the molecular target of nitrogen-containing bisphosphonates inside the osteoclast?
1. RANKL
2. Farnesyl pyrophosphate synthase in the mevalonate pathway
3. The PTH type 1 receptor
4. Carbonic anhydrase
1. Explanation: Nitrogen-containing bisphosphonates such as alendronate and zoledronic acid inhibit farnesyl pyrophosphate synthase, impairing the prenylation osteoclasts need for their cytoskeleton and driving them to apoptosis. [6]
2. Question: Why must oral bisphosphonates be taken on an empty stomach with plain water and followed by remaining upright?
1. To increase the drug's half-life
2. Because oral bioavailability is extremely low and reduced further by food, other beverages or medication, and because of esophageal irritation risk
3. Because the drug is destroyed by stomach acid otherwise
4. To prevent hypocalcemia
2. Explanation: Oral bisphosphonate bioavailability is under 1% even under ideal fasting conditions and is reduced further by co-ingested food, drink or medication; remaining upright reduces esophageal reflux of the drug and the associated irritation risk. [1]
3. Question: Which of the following is a labelled risk specifically of stopping denosumab, rather than of continuing it?
1. Osteonecrosis of the jaw
2. Rebound increase in bone turnover with increased vertebral fracture risk
3. Acute-phase reaction
4. Hypercalcemia
3. Explanation: Because denosumab's effect is not stored in bone the way a bisphosphonate's is, stopping it causes bone turnover to rebound, with an increased risk of vertebral fracture, including multiple vertebral fractures - the label calls for transitioning to another antiresorptive rather than simple discontinuation. [3]
4. Question: What mechanistically distinguishes teriparatide and abaloparatide from the bisphosphonates and

denosumab?

1. They are given orally
2. They are antiresorptive like the others but longer-acting
3. They act as agonists at the PTH type 1 receptor and are anabolic, stimulating new bone formation rather than only slowing resorption
4. They have no labelled long-term risks
4. Explanation: Teriparatide (PTH(1-34)) and abaloparatide (a PTHrP(1-34) analog) activate the PTH1 receptor on osteoblasts; given intermittently this favours new bone formation, the opposite direction from the antiresorptive bisphosphonates and denosumab. [4][5]
5. Question: Zoledronic acid is contraindicated at what level of renal function?
 1. Creatinine clearance below 60 mL/min
 2. Creatinine clearance below 35 mL/min, or acute renal impairment
 3. Any degree of chronic kidney disease
 4. There is no renal contraindication
5. Explanation: Reclast (zoledronic acid) is contraindicated in patients with creatinine clearance below 35 mL/min or evidence of acute renal impairment, reflecting its renal elimination pathway and reports of acute renal failure with the drug. [2]
6. Question: What finding in animal studies led both teriparatide and abaloparatide to carry a two-year lifetime-use limitation?
 1. Hepatotoxicity in dogs
 2. Dose-dependent increases in osteosarcoma in rats
 3. Renal failure in primates
 4. QT prolongation in guinea pigs
6. Explanation: Both drugs caused a dose- and duration-dependent increase in osteosarcoma incidence in rats at exposures well above the human clinical dose, and it is unknown whether this translates to humans, which is why both labels cap lifetime use at two years. [4][5]

Frequently asked questions

1. Question: Is denosumab a type of bisphosphonate?
 1. Answer: No. Denosumab is a monoclonal antibody that binds RANKL, a signal osteoclast precursors need to mature into resorbing cells. It is grouped with the bisphosphonates on this page because it is used for the same clinical problem - antiresorptive treatment of osteoporosis - but its chemistry, dosing route and, importantly, its discontinuation risk are all genuinely different from any bisphosphonate. [3]
2. Question: Why is the oral bisphosphonate dosing instruction so strict?
 2. Answer: Oral bioavailability is inherently very low, well under 1%, and any co-ingested food, other beverage, or medication reduces it further, so the empty-stomach, plain-water, stay-upright instruction is what makes the dose actually absorbed rather than merely a comfort measure. It also reduces esophageal exposure to the drug, lowering the risk of esophagitis. [1]
3. Question: What happens if a patient stops denosumab abruptly?
 3. Answer: Bone turnover rebounds because denosumab's antiresorptive effect is not stored in bone the way a bisphosphonate's is. The label associates stopping denosumab with an increased risk of vertebral fracture, including multiple vertebral fractures occurring close together, which is why the recommended approach is to transition to another antiresorptive agent rather than simply discontinuing treatment. [3]
4. Question: Why do teriparatide and abaloparatide have a two-year lifetime limit when bisphosphonates don't?
 4. Answer: Both drugs caused a dose- and duration-dependent increase in osteosarcoma in rat carcinogenicity studies at high, prolonged exposures. It is not established whether this risk occurs in humans at the doses used clinically, but both labels respond to the animal finding by capping lifetime treatment at two years and by advising against use in

patients who already have other osteosarcoma risk factors, such as Paget's disease of bone or prior skeletal radiation.
[4][5]

References

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