Therapeutic Class Overview
Intranasal Calcitonins

Therapeutic Class Overview/Summary:
Osteoporosis is the most common bone disease in humans and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture.[1] According to the World Health Organization, osteoporosis is defined by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the expected average for a healthy young person.[2] Utilizing a reference population of young healthy individuals is common when measuring BMD and is known as a T-score.[1] Fractures are the most clinically significant physical manifestation of postmenopausal osteoporosis and low bone mass is the primary indicator of fracture risk.[3] Osteoporotic fractures commonly occur in the wrist, spine, or hip, and can result in complications such as chronic pain, disability, depression, or even death.[1] Osteoporosis and related fractures represent a significant public health and economic burden. The management of osteoporosis is intended to prevent initial or subsequent fractures by maximizing skeletal strength and/or minimizing skeletal trauma, as well as increase the patient's quality of life.[3]

Calcitonin-salmon, a calcitonin derivative, is a polypeptide containing 32 amino acids in the same linear sequence as endogenous calcitonin. Endogenous calcitonin acts primarily on bone; however, direct renal and gastrointestinal effects have also been observed. Calcitonin-salmon appears to have similar actions but has a greater potency and duration of action compared to endogenous calcitonin. The actions of calcitonin on bone and its role in normal human bone physiology are not completely understood, although calcitonin receptors have been discovered in osteoclasts and osteoblasts. Information derived from clinical trials evaluating injectable calcitonin-salmon suggest the agents in this medication class cause marked transient inhibition of the ongoing bone resorptive process.[4,5]

Calcitonin-salmon is currently available as an injection, which is administered either subcutaneously or intramuscularly, or nasal spray. Only the nasal spray formulation will be covered in this review. Miacalcin® (calcitonin-salmon) nasal spray is manufactured by chemical synthesis, and Fortical® (calcitonin-salmon) nasal spray is manufactured by recombinant deoxyribonucleic acid technology and is identical to the synthetic formulations.[4,5] Nasal calcitonin-salmon is only FDA-approved for the treatment of postmenopausal osteroporosis.[4,5] The calcitonins are for use only in postmenopausal women greater than five years postmenopause with low bone mass relative to healthy premenopausal females.[4,5] Currently, synthetic nasal calcitonin-salmon is the only calcitonin available generically.

While not every guideline recommends a preferred medication and/or medication class, the bisphosphonates are generally recognized as first-line therapy for the prevention and treatment of osteoporosis, including postmenopausal and glucocorticoid-induced osteoporosis.[1,3,6-9]

Table 1. Current Medications Available in the Therapeutic Class[4,5]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
calcitonin-salmon rDNA origin (Fortical®)	Treatment of postmenopausal osteoporosis in women greater than five years postmenopause with low bone mass relative to healthy premenopausal females†		-
calcitonin-salmon synthetic (Miacalcin®*)	Treatment of postmenopausal osteoporosis in women greater than five years postmenopause with low bone mass relative to healthy premenopausal females†		a

*Generic available in at least one dosage form or strength.
† Use is recommended in conjunction with adequate calcium and vitamin D intake to prevent the progressive loss of bone mass. Use should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated.

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Evidence-based Medicine

- Overall, there is a lack of substantial clinical trial data for this medication class, as trials are typically small in size and observational in design.[10-13]
- A meta-analysis of 30 clinical trials demonstrated that calcitonins significantly decreased the risk of vertebral fractures compared to control (placebo or calcium and/or vitamin D); however, there was no significant difference in the risk for non-vertebral fractures.[13]
- Nasal calcitonin-salmon was no different than placebo for adverse events other than rhinitis.[10-13]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options, with the bisphosphonates having good quality evidence supporting their use for reducing the risk of vertebral, non-vertebral, and hip fractures.
  - Bisphosphonates are considered first-line[1,3,6-9]
  - Calcitonins are recognized as a potential option for the treatment of osteoporosis, have a fair quality evidence to support their use in reducing vertebral fractures.[6]
  - For postmenopausal osteoporosis, calcitonins are recommended as a last line therapy, and no product is recommended or preferred over another.[3,7,8]
- Other Key Facts:
  - Calcitonin-salmon may also be used off-labeled for cancer pain, treatment of glucocorticoid-induced osteoporosis, and for prophylaxis of fracture of bone in patients with osteoporosis.[14]
  - There are no clinically significant drug interactions associated with the calcitonins.[15]

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Therapeutic Class Review
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Overview/Summary

Osteoporosis is the most common bone disease in humans and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture.[1] According to the World Health Organization, osteoporosis is defined by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the expected average for a healthy young person.[2] Utilizing a reference population of young healthy individuals is common when measuring BMD and is known as a T-score.[1] Fractures are the most clinically significant physical manifestation of postmenopausal osteoporosis and low bone mass is the primary indicator of fracture risk.[3] Osteoporotic fractures commonly occur in the wrist, spine, or hip, and can result in complications such as chronic pain, disability, depression, or even death.[1] Osteoporosis and related fractures represent a significant public health and economic burden. The management of osteoporosis is intended to prevent initial or subsequent fractures by maximizing skeletal strength and/or minimizing skeletal trauma, as well as increase the patient's quality of life.[3]

Calcitonin-salmon, a calcitonin derivative, is a polypeptide containing 32 amino acids in the same linear sequence as endogenous calcitonin. Endogenous calcitonin acts primarily on bone; however, direct renal and gastrointestinal effects have also been observed. Calcitonin-salmon appears to have similar actions but has a greater potency and duration of action compared to endogenous calcitonin. The actions of calcitonin on bone and its role in normal human bone physiology are not completely understood, although calcitonin receptors have been discovered in osteoclasts and osteoblasts. Information derived from clinical trials evaluating injectable calcitonin-salmon suggest the agents in this medication class cause marked transient inhibition of the ongoing bone resorptive process.[4,5]

Calcitonin-salmon is currently available as an injection, which is administered either subcutaneously or intramuscularly, or nasal spray. Only the nasal spray formulation will be covered in this review. Miacalcin® (calcitonin-salmon) nasal spray is manufactured by chemical synthesis, and Fortical® (calcitonin-salmon) nasal spray is manufactured by recombinant deoxyribonucleic acid technology and is identical to the synthetic formulations.[4,5] Nasal calcitonin-salmon is only FDA-approved for the treatment of postmenopausal osteroporosis.[4,5] The calcitonins are for use only in postmenopausal women greater than five years postmenopause with low bone mass relative to healthy premenopausal females.[4,5] Currently, synthetic nasal calcitonin-salmon is the only calcitonin available generically.

Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options, with the bisphosphonates having good quality evidence supporting their use for reducing the risk of vertebral, non-vertebral, and hip fractures. While not every guideline recommends a preferred medication and/or medication class, the bisphosphonates are generally recognized as first-line therapy for the prevention and treatment of osteoporosis, including postmenopausal and glucocorticoid-induced osteoporosis.[1,3,6-9] Calcitonins are recognized as a potential option for the treatment of osteoporosis, have a fair quality evidence to support their use in reducing vertebral fractures.[6] For postmenopausal osteoporosis, calcitonins are recommended as a last line therapy, and no product is recommended or preferred over another.[3,7,8]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Calcitonin-salmon (rDNA origin) (Fortical®)	Calcitonins	-
Calcitonin-salmon (synthetic) (Miacalcin®*)	Calcitonins	a

rDNA=recombinant deoxyribonucleic acid
*Generic available in at least one dosage form or strength.

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Indications

Table 2. Food and Drug Administration-Approved Indications[4,5]

Indication	Calcitonin-Salmon (rDNA Origin)	Calcitonin-Salmon (Synthetic)
Treatment of postmenopausal osteoporosis in women greater than five years postmenopause with low bone mass relative to healthy premenopausal females†	a *	a *

rDNA=recombinant deoxyribonucleic acid
*Use is recommended in conjunction with adequate calcium and vitamin D intake to prevent the progressive loss of bone mass.
†Should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated.

In addition, calcitonin-salmon may also be used off-labeled as adjunctive treatment for cancer pain, treatment of glucocorticoid-induced osteoporosis, and for prophylaxis of fracture of bone in patients with osteoporosis.[10]

Pharmacokinetics

The pharmacokinetic properties of nasal calcitonin-salmon manufactured by recombinant deoxyribonucleic acid technology were shown to be similar to that of a commercially available calcitonin-salmon product in healthy volunteers.[4]

Table 3. Pharmacokinetics[10]

Generic Name	Bioavailability (%)	Time to Peak Concentration (minutes)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Calcitonin-salmon	3	31 to 39	Not reported	None	0.7

Clinical Trials

Clinical trials demonstrating the safety and efficacy of calcitonins in Food and Drug Administration-approved indications are outlined in Table 4. Overall, there is a lack of substantial clinical trial data for this medication class, as trials are typically small in size and observational in design.[11-14]

Nasal calcitonin-salmon achieved significant increases in bone mineral density (BMD) at the lumbar spine compared to placebo after six months of therapy, which was maintained for up to two years. Effects on BMD at the forearm and hip have produced mixed results with some trials demonstrating improvement, or preservation, and others demonstrating no improvement.[11-13] Furthermore, a meta-analysis of 30 clinical trials demonstrated that calcitonins significantly decreased the risk of vertebral fractures compared to control (placebo or calcium and/or vitamin D); however, there was no significant difference in the risk for non-vertebral fractures.[14] There is a lack of substantial head-to-head data comparing calcitonins to other established osteoporosis's treatments. In two clinical trials, bisphosphonate therapy and parathyroid hormone therapy demonstrated significantly greater increases in BMD at the lumbar spine compared to nasal calcitonin-salmon.[13]

In terms of safety data, no clinically significant concerns related to the calcitonins were observed. With nasal calcitonin-salmon, adverse events were no different than placebo, with the exception of rhinitis.[11-14]

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Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Postmenopausal Osteoporosis				
Chestnut et al[11] PROOF Calcitonin 100, 200, or 400 IU/day nasal spray vs placebo All patients received daily calcium and vitamin D supplements.	DB, MC, PC, RCT Postmenopausal women with osteoporosis but no history of hip fracture	N=1,255 5 years	Primary: Incidence of new vertebral fractures Secondary: Incidence of new non-vertebral fractures, change in baseline lumbar spine BMD and BTMs, safety	Primary: During the trial, 1,108 patients had at least one follow-up radiograph. A total of 783 patients completed three years of treatment, and 511 patients completed five years of treatment. Calcitonin 200 IU/day significantly reduced the risk of new vertebral fractures by -33% compared to placebo (51 vs 70 cases; RR, 0.67; 95% CI, 0.47 to 0.97; P=0.03). In the 817 patients with one to five prevalent vertebral fractures at baseline, the risk was significantly reduced by -36% (RR, 0.64; 95% CI, 0.43 to 0.96; P=0.03). Calcitonin 100 (RR, 0.85; 95% CI, 0.60 to 1.21) and 400 IU/day (RR, 0.84; 95% CI, 0.59 to 1.18) did not significantly reduce the risk of vertebral fractures compared to placebo (P values not reported). Secondary: Compared to placebo, the proportions of patients with non-vertebral fractures were significantly lower with calcitonin 100 IU/day (P<0.05), but not with 200 or 400 IU/day (P values not reported). BMD at the lumbar spine increased significantly (1.0 to 1.5%; P<0.01) with all calcitonin doses at each time point during the five year trial. No effect of treatment on BMD at the femoral or trochanter was observed (P values not reported). Bone turnover was inhibited as shown by a decrease in SCTX (bone resorption marker) by -12% with calcitonin 200 IU/day (P<0.01) and by -14% with calcitonin 400 IU/day (P<0.01) compared to placebo. The distribution of adverse effects was similar between calcitonin and placebo, except for a significant increase in rhinitis, which had a significantly higher incidence with calcitonin (22 vs 15%; P<0.01).
Chestnut et al[12] QUEST	DB, PC, RCT	N=91	Primary: Assess trabecular	Primary: In the distal radius and lower trochanter of the hip, calcitonin exhibited

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Calcitonin 200 IU/day nasal spray vs placebo All patients received daily calcium supplements.	Postmenopausal osteoporotic women	2 years	microarchitecture at multiple skeletal sites Secondary: Not reported	significant preservation (no significant loss) of trabecular bone microarchitecture compared to placebo, where significant deterioration was shown. At the distal radius, significant improvement or preservation was reported in apparent trabecular volume (P<0.03), apparent trabecular number (P<0.01), and apparent trabecular spacing (P<0.01) with calcitonin compared to placebo. At the hip, calcitonin exhibited preservation of trabecular microarchitecture at the lower trochanter (P<0.05). Significant deterioration of trabecular bone architecture was observed with placebo at the femoral neck, Ward's triangle, and lower trochanteric sites (P values not reported). Analysis of iliac crest bone biopsies did not reveal significant differences between treatments (P values not reported). Regardless of changes in BMD (gain or loss at the spine, hip, or distal radius), preservation of parameters of trabecular microarchitecture was observed with calcitonin, whereas loss or preservation was observed with placebo (P values not reported). SCTX (bone resorption marker) was decreased by -22.5% at 24 months (P=0.056) with calcitonin. Secondary: Not reported
Downs et al[13] Calcitonin 200 IU/day nasal spray vs alendronate 10 mg/day vs	MC, PC, PRO, RCT Women ≥5 years postmenopause with osteoporosis	N=299 1 year	Primary: Change in baseline lumbar spine BMD Secondary: Change in baseline femoral neck and hip trochanter BMD,	Primary: Alendronate significantly increased BMD at the lumbar spine compared to calcitonin (5.16 vs 1.18%; P<0.001). There was no difference between calcitonin and placebo (P value not reported). Secondary: Alendronate significantly increased BMD at the femoral neck (2.78 vs 0.58%; P<0.001) and hip trochanter (4.73 vs 0.47%; P<0.001) compared to calcitonin.

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Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo All patients received daily calcium and vitamin D supplements.			and BTMs	Calcitonin significantly increased BMD at the femoral neck at months six and 12 compared to placebo (P<0.0.01), but there was no difference at hip trochanter (P value not reported). Significantly greater decreases in BTMs were observed with alendronate compared to calcitonin (serum bone alkaline phosphatase, -43 vs -9%; P<0.001; N-telopeptide, -62 vs -11%; P<0.001). No differences were observed between calcitonin and placebo (P values not reported). The incidences of adverse events were similar among the treatments.
Cranney et al[14] Osteoporosis Methodology Group and Osteoporosis Research Advisory Group Calcitonin, doses varied and routes included intranasal, IM, SC, and rectal, with or without calcium and/or vitamin D vs placebo or calcium and/or vitamin D	MA (30 RCTs) Postmenopausal women receiving treatment for either the prevention or treatment of osteoporosis	N=3,993 ≥1 year	Primary: Incidence of vertebral and non-vertebral fractures, changes in baseline BMD Secondary: Not reported	Primary: Only results for calcitonin are reported. The incidence of vertebral fractures was reduced with calcitonin compared to control (RR, 0.46; 95% CI, 0.25 to 0.87; P=0.02). There was no difference in the risk for non-vertebral fractures with calcitonin and control (RR, 0.52; 95% CI, 0.22 to 1.23; P=0.14). Calcitonin 250 to 2,800 IU/week significantly increased BMD at the lumbar spine (WMD, 3.74; 95% CI, 2.04 to 5.43; P<0.01). Calcitonin 350 to 2,800 IU/week significantly increased BMD at the forearm (WMD, 3.02; 95% CI, 0.98 to 5.07; P<0.01). At the femoral neck, there was an improvement in BMD with calcitonin (WMD, 3.80; 95% CI, -0.32 to 7.91; P=0.07). Secondary: Not reported

Drug regimen abbreviations: IU=international units QD=once-daily
Study design abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-labeled, OS=observational study, PC=placebo-controlled, PRO=prospective, RCT=randomized-controlled trial, RETRO=retrospective, RR=relative risk, WMD=weighted mean difference
Miscellaneous abbreviations: BMD=bone mineral density, BTM=bone turnover marker, SCTX=serum type-1 collagen cross-linked C-telopeptide

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Special Populations

Table 5. Special Populations[4,5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Calcitonin-salmon	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established. †	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown; use with caution.

†Disorders of bone in children referred to as idiopathic juvenile osteoporosis have been reported rarely. The relationship of these disorders to postmenopausal osteoporosis has not been established and experience with the use of calcitonin in these disorders is very limited. There are no data to support the use of calcitonin nasal spray in children.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[4,5]

Adverse Event(s)	Calcitonin-Salmon
Anemia	1 to 3
Angina pectoris	1 to 3
Bundle branch block	1 to 3
Hypertension	1 to 3
Myocardial infarction	1 to 3
Palpitation	1 to 3
Tachycardia	1 to 3
Agitation	1 to 3
Anxiety	1 to 3
Depression	1 to 3
Dizziness	1 to 3
Fatigue	1 to 3
Headache	3.2
Insomnia	1 to 3
Migraine	1 to 3
Neuralgia	1 to 3
Paresthesia	1 to 3
Vertigo	1 to 3
Goiter	1 to 3
Hyperthyroidism	1 to 3
Abdominal pain	1 to 3
Anorexia	1 to 3
Constipation	1 to 3
Diarrhea	1 to 3
Dry mouth	1 to 3
Dyspepsia	1 to 3
Flatulence	1 to 3
Gastritis	1 to 3
Increased appetite	1 to 3
Nausea	1 to 3
Vomiting	1 to 3
Cystitis	1 to 3
Hematuria	1 to 3

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Adverse Event(s)	Calcitonin-Salmon
Pyelonephritis	1 to 3
Renal calculus	1 to 3
Allergic rhinitis	1 to 3
Epistaxis	3.5
Nasal congestion	1 to 3
Nasal odor	1 to 3
Rhinitis	12
Rhinitis ulcerative	1 to 3
Sinusitis	1 to 3
Sneezing	1 to 3
Symptom of nose*	10.6
Cholelithiasis	1 to 3
Hepatitis	1 to 3
Thirst	1 to 3
Weight increase	1 to 3
Arthralgia	3.8
Arthritis	1 to 3
Arthrosis	1 to 3
Back pain	5
Myalgia	1 to 3
Polymyalgia rheumatica	1 to 3
Stiffness	1 to 3
Bronchitis	1 to 3
Bronchospasm	1 to 3
Coughing	1 to 3
Dyspnea	1 to 3
Mucosal ulceration	1 to 3
Parosmia	1 to 3
Pharyngitis	1 to 3
Pneumonia	1 to 3
Taste perversion	1 to 3
Upper respiratory tract infection	1 to 3
Abnormal lacrimation	1 to 3
Alopecia	1 to 3
Blurred vision	1 to 3
Cerebrovascular accident	1 to 3
Conjunctivitis	1 to 3
Earache	1 to 3
Eczema	1 to 3
Edema	1 to 3
Erythematous rash	1 to 3
Fatigue	1 to 3
Flushing	1 to 3
Hearing loss	1 to 3
Increased sweating	1 to 3
Infection	1 to 3
Influenza-like symptoms	1 to 3
Lymphadenopathy	1 to 3
Pruritus	1 to 3
Skin ulceration	1 to 3
Thrombophlebitis	1 to 3

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Adverse Event(s)	Calcitonin-Salmon
Tinnitus	1 to 3
Visual disturbance	1 to 3
Vitreous floater	1 to 3

*Symptom of nose includes nasal crusts, sores, dryness, redness, irritation, itching, tenderness, pallor, infection, stenosis, discharge or blockage, and small or bleeding wound.

Contraindications/Precautions

Calcitonins are contraindicated with allergy to calcitonin-salmon.[4,5]

Because calcitonin-salmon is a polypeptide, the possibility of allergic reaction exists, and a few cases of serious allergic-type reactions have been reported in patients receiving calcitonins. The usual provisions should be made for emergency treatment if such a reaction should occur. Allergic reactions should be differentiated from generalized flushing and hypotension. Skin testing should be considered prior to treatment initiation for patients with suspected sensitivity to calcitonins. In addition, patients should seek emergency medical help if any of the following symptoms of serious allergic reaction occur: trouble breathing; swelling of the face, throat, or tongue; rapid heartbeat; chest pain; and feeling faint or dizzy.[4,5]

Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum, and mucosal blood vessel status are recommended with nasal calcitonin-salmon. In addition, a nasal examination should be performed prior to start of treatment with nasal calcitonin-salmon and at any time nasal complaints occur. If severe ulceration of the nasal mucosa occurs, nasal calcitonin-salmon should be discontinued. Although smaller ulcers often heal without withdrawal of treatment, medication should be discontinued temporarily until healing occurs.[4,5]

Periodic examinations of urine sediment of patients on chronic therapy are recommended.[4,5]

Careful instruction in sterile injection technique should be given to the patient, and to other persons who may administer injectable calcitonin-salmon. Careful instructions on pump assembly, priming of the pump, and nasal introduction of nasal calcitonin-salmon should be given to patients.[4,5]

An increased incidence of non-functioning pituitary adenomas has been observed in a one year, rate toxicity trial. The relevance of these findings to humans is unknown.[4,5]

Drug Interactions

There are no clinically significant drug interactions associated with the calcitonins.[15]

Dosage and Administration

Table 7. Dosing and Administration[4,5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Calcitonin-salmon	Treatment of postmenopausal osteoporosis in women greater than five years postmenopause with low bone mass relative to healthy premenopausal females : Nasal spray: 200 IU once daily; alternating nostrils daily	Safety and efficacy in children have not been established.	Nasal spray: 200 IU/ actuation

IU=international units

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*Preferred for outpatient self-administration.

Clinical Guidelines

Current clinical guidelines are summarized in Table 8. Please note that guidelines addressing the prevention and treatment of osteoporosis are presented globally, addressing the role of various medication classes.

Table 8. Clinical Guidelines Using the Calcitonins

Clinical Guideline	Recommendations
National Osteoporosis Foundation: **Clinician's Guide to Prevention and Treatment of Osteoporosis (2013)**[1]	Synopsis of major recommendations · The following recommendations apply to postmenopausal women and men ≥50 years of age. · Patients should be counseled on the risk of osteoporosis and related fractures. · Secondary causes of osteoporosis should be assessed in patients. · Patients should be advised to supplement with adequate amounts of calcium (1,000 mg/day for men 50 to 70 years; ≥1,200 mg/day for women 51 years and older and men 71 years or older) and vitamin D (800 to 1,000 international units [IU]/day), including supplements if necessary for patients ≥50 years of age. · Regular weight-bearing and muscle-strengthening exercises should be recommended to reduce the risk of falls and fractures. · Tobacco smoking and excessive alcohol intake should be avoided. · Bone mineral density (BMD) testing is recommended in women ≥65 years of age and men ≥70 years of age. · In postmenopausal women and men 50 to 69 years of age, recommend BMD testing when you have concern based on their risk factor profile. · A BMD test is recommended to those who have had a fracture, in order to determine the degree of disease severity. · Vertebral imaging should be performed for certain patients based on BMD t-score · Treatment should be initiated in patients with hip or vertebral (clinical or asymptomatic) fractures. · Initiate therapy in those patients with BMD T-scores ≤-2.5 at the femoral neck or spine by dual-energy x-ray absorptiometry, after appropriate evaluation. · Initiate treatment in postmenopausal women and men ≥50 years of age with low bone mass (T-score -1.0 to -2.5, osteopenia) at the femoral neck or spine and a 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability ≥20% based on the United States-adapted World Health Organization absolute fracture risk model. · Current Food and Drug Administration (FDA)-approved pharmacologic options for osteoporosis prevention and/or treatment are bisphosphonates (alendronate, ibandronate, risedronate, zoledronic acid), calcitonin, estrogen agonist/antagonist (raloxifene), estrogens and/or hormone therapy, tissue-selective estrogen complex (conjugated estrogens/bazedoxifene), parathyroid hormone (teriparatide), and RANK ligand inhibitor (denosumab). · No pharmacologic therapy should be considered indefinite in duration. After the initial treatment period, which depends on the pharmacologic agent, a comprehensive risk assessment should be performed. There is no uniform recommendation that applies to all patients and duration decisions need to be individualized

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Clinical Guideline	Recommendations
	· BMD testing performed in dual-energy x-ray absorptiometry centers using accepted quality assurance measures is appropriate for monitoring bone loss. For patients on pharmacotherapy, it is typically performed two years after initiating therapy and every two years thereafter; however, more frequent testing may be warranted in certain clinical solutions.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis (2010)**[3]	Prevention of bone loss · Maintain adequate calcium and vitamin D intake. Use calcium supplements, if needed, to meet minimal required intake. Supplement vitamin D, if needed, to maintain serum levels of 25-hydroxyvitamin D 30 to 60 ng/mL. · Limit alcohol intake (≤2 servings/day). · Limit caffeine intake. · Avoid or stop smoking. · Maintain an active lifestyle, including weight bearing exercises for ≥30 minutes a day. Nonpharmacologic treatment · In addition to the preventative measures, patients should maintain adequate protein intake, use proper body mechanics, consider the use of hip protectors (individuals with a high risk of falling), take measures to reduce the risk of falling, and consider physical and occupational therapy. Screening for osteoporosis · Women ≥65 years of age and younger postmenopausal women at an increased risk of fracture should be screened for osteoporosis. Diagnosis and evaluation of osteoporosis · A central dual-energy x-ray absorptiometry measurement should be used to diagnosis osteoporosis. · In the absence of fracture, osteoporosis is defined as a T-score ≤-2.5 in the spine, femoral neck or total hip. · Osteoporosis is defined as the presence of a fracture of the hip or spine (in the absence of other bone conditions). · Evaluation for secondary osteoporosis should occur. · Clinicians should also evaluate prevalent vertebral fractures. Pharmacologic therapy · Patients with a history of a fracture of the hip or spine should receive pharmacologic therapy. · Patients with a history of fractures but with a T-score ≤-2.5 should receive pharmacologic therapy. · Patients with a T-score -1.0 to -2.5 and a FRAX® (a tool created by the World Health Organization) major osteoporotic fracture probability ≥20% or a hip fracture probability of at least 3% should receive pharmacologic therapy. · Drugs with proven anti-fracture efficacy should be used. · Use alendronate, risedronate, zoledronic acid, and denosumab as first-line therapy. · Use ibandronate as a second-line therapy. · Use raloxifene as a second- or third-line therapy. · Use calcitonin as last line of therapy.

Clinical Guideline	Recommendations
	· Use teriparatide for patients with very high fracture risk or in patients who have failed bisphosphonate therapy. · Combination therapy is not recommended. Monitoring treatment · Obtain a baseline dual-energy x-ray absorptiometry, and repeat every one to two years until findings are stable. Continue with follow up dual-energy x-ray absorptiometry every two years or at a less frequent interval. · Changes in spine or total hip BMD should be monitored. · Follow-up of patients should be in the same facility, with the same machine, and, if possible, with the same technologist. · Bone turnover markers may be used at baseline to identify patients with high bone turnover and can be used to follow the response to therapy. Successful treatment · Treatment can be considered successful if BMD is stable or increasing, and no fractures are present. · Treatment can be considered successful if bone turnover makers are at or below the median value for premenopausal women for patients taking antiresorptive agents. · One fracture is not necessarily evidence of failure. Consider alternative therapy or reassessment for secondary causes of bone loss for patients who have recurrent fractures while receiving therapy. Duration of treatment · For treatment with bisphosphonates, if osteoporosis is mild, consider a "drug holiday" after four to five years of stability. If fracture risk is high, consider a drug holiday of one to two years after 10 years of treatment. · Follow BMD and bone turnover markers during a drug holiday period, and reinitiate therapy if bone density declines substantially, bone turnover markers increase, or a fracture occurs. Referral to a clinical endocrinologist · When a patient with normal BMD sustains a fracture without major trauma. · When recurrent fractures or continued bone loss occurs in a patient receiving therapy without obvious treatable causes of bone loss. · When osteoporosis is unexpectedly severe or has unusual features. · When a patient has a condition that complicates management (e.g., renal failure, hyperparathyroidism, malabsorption).
American College of Physicians: **Pharmacologic Treatment of Low Bone Density or Osteoporosis to Prevent Fractures: A Clinical Practice Guideline From the American College of Physicians (2008)**[6]	Initiating treatment · Pharmacologic treatment should be offered to men and women who have known osteoporosis and to those who have experienced fragility fractures. o Good quality evidence demonstrates that bisphosphonates, estrogen, raloxifene, and teriparatide prevent vertebral fractures. Fair quality evidence demonstrates that calcitonin reduces vertebral fractures. o Good quality evidence also supports that bisphosphonates and estrogen prevent non-vertebral and hip fractures. Calcitonin and raloxifene have not been demonstrated to reduce non-vertebral and hip fractures. The evidence related to teriparatide is mixed

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	with one large trial demonstrating a reduction and two small trials not demonstrating a reduction in non-vertebral fractures. Teriparatide has not demonstrated a reduction in hip fractures. · Pharmacologic treatment should be considered for men and women who are at risk for developing osteoporosis (patients with a T-score -1.5 to -2.5, are receiving glucocorticoids, or are >62 years). <u>Pharmacologic therapies for the prevention and treatment of osteoporosis</u> · The drugs currently FDA-approved for the prevention of osteoporosis include bisphosphonates, estrogen, and raloxifene. The drugs currently FDA-approved for the treatment of osteoporosis include bisphosphonates, calcitonin, raloxifene, and teriparatide. · Selection of pharmacologic treatment options for osteoporosis in men and women should be based on assessment of the risks and benefits to the individual patients. o Because good-quality evidence demonstrates that bisphosphonates reduce the risk for vertebral, non-vertebral, and hip fractures, they are reasonable options to consider as first-line therapy (particularly in patients at a high risk for a hip fracture). Of the other agents available for treatment of osteoporosis, estrogen reduces the incidence of vertebral, non-vertebral, and hip fractures, but is associated with other serious risks. o The most common adverse events associated with bisphosphonates are related to the gastrointestinal tract. No evidence was found that bisphosphonates, calcitonin, calcium, teriparatide, and vitamin D differ in risk for serious cardiac events. Estrogen was associated with a greater risk for stroke, and the estrogen-progestin combination was associated with a greater probability of stroke and higher odds of breast cancer. Raloxifene was associated with a higher risk for pulmonary embolism, thromboembolic events, and mild cardiac events. o Evidence is insufficient to determine whether one bisphosphonate is “superior” to another. o No clear evidence demonstrates the appropriate duration of treatment with bisphosphonates.
North American Menopause Society: **Management of Osteoporosis in Postmenopausal Women: 2010 Position Statement of The North American Menopause Society (2010)**[7]	· All postmenopausal women should be encouraged to employ lifestyle practices that reduce the risk of bone loss and osteoporotic fractures: maintain a healthy weight, eat a balanced diet, obtain adequate calcium and vitamin D, participate in appropriate exercise, avoid excessive alcohol consumption, do not smoke, and utilize measures to prevent falls. · Periodic reviews of calcium and vitamin D intake and lifestyle behaviors are useful. · After menopause, a woman’s risk of falls should be assessed annually and at any time her physical or mental status changes. · The physical examination should include an annual measurement of height and weight, along with an assessment from chronic back pain, kyphosis, and clinical risk factors. · BMD testing is indicated for all postmenopausal women with medical causes of bone loss, and all women ≥65 years of age. · BMD testing should be considered for postmenopausal women ≥50 years of age who have one or more of the following risk factors: previous fractures (other than skull, facial bone, ankle, finger, and toe) after

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	menopause, thinness (body weight <127 lbs or a body mass index <21 kg/m^2), history of hip fracture in a parent, current smoking, rheumatoid arthritis, and excessive alcohol intake. · When BMD testing is indicated, dual-energy x-ray absorptiometry is the preferred technique. The total hip, femoral neck, and posterior-anterior lumbar spine should be measured, using the lowest of the three BMD scores. · The routine use of biochemical markers of bone turnover in clinical practice is not generally recommended. · Vertebral fracture must be confirmed by lateral spine radiographs or vertebral fracture assessment visualization of fracture at the time of BMD testing. Vertebral fracture is confirmed by height loss >20% of the anterior, mid, or posterior dimension of a vertebra on imaging. · An adequate intake of both calcium and vitamin D is important for bone health and is recognized as an important component of any osteoporosis prescription-drug regimen. North American Menopause Society follows the National Osteoporosis Foundation recommendations of calcium intake of 1,200 mg/day for adults ≥50 years of age, and vitamin D_3 of 800 to 1,000 IU/day. · Osteoporosis drug therapy is recommended in the following populations: all postmenopausal women who have had an osteoporotic vertebral or hip fracture; all postmenopausal women who have BMD values consistent with osteoporosis at the lumbar spine, femoral neck, or total hip region; and all postmenopausal women who have T-scores -1.0 to -2.5 and a 10-year risk, based on the FRAX® calculator, of major osteoporotic fracture of at least 20% or of hip fracture of at least 3%. · It is important to encourage adherence to the treatment plan and to identify barriers to nonadherence. Providing clear information to women regarding their risk for fracture and the purpose of osteoporosis therapy may be the optimal way to improve adherence. · During therapy, it is appropriate to re-evaluate the treatment goals and the choice of medication on an ongoing basis through periodic medical examination and follow-up BMD testing. Measurement of BMD has limited use in predicting the effectiveness of antiresorptive therapies for reducing fracture risk. Also, fracture risk reductions from therapy occur much more rapidly than BMD changes. An appropriate interval for repeat BMD testing is after one to two years of treatment. There appears to be little value in repeat testing if a woman is stable. · For untreated postmenopausal women, repeat dual-energy x-ray absorptiometry testing is not useful until two to five years have passed. · Bisphosphonates are the first-line drugs for treating postmenopausal women with osteoporosis. They have reduced the risk of vertebral fractures by 40 to 70% and reduced the incidence of non-vertebral fracture, including hip fracture, by about half this amount. · The selective estrogen-receptor modulator raloxifene is most often considered for postmenopausal women with low bone mass or younger postmenopausal women with osteoporosis. It prevents bone loss and reduces the risk of vertebral fractures, but its effectiveness in reducing other fractures is uncertain. Extraskeletal risks and benefits are important when considering raloxifene therapy. · Teriparatide is best offered to postmenopausal women with osteoporosis who are at high risk for fracture. Daily subcutaneous injections have been

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	shown to stimulate bone formation and improve bone density. Therapy is indicated for no more than 24 months. · The primary indication for systemic estrogen or estrogen plus progestogen therapy is to treat moderate-to-severe menopause symptoms. When symptoms are controlled or cease, continued hormone therapy can still be considered for bone effects, weighing its benefits and risks against those of alternative therapies. · Estrogen and estrogen plus progestogen therapy may be a treatment option for a few years of early postmenopause. · Calcitonin is not a first-line drug for postmenopausal osteoporosis treatment, as its fracture efficacy is not strong and its BMD effects are less than those of other agents. However, it is an option for women with osteoporosis who are more than five years beyond menopause. · Calcitonin therapy may reduce vertebral fracture risk in women with osteoporosis, although the evidence documenting fracture protection is not strong. It is not recommended for treating bone pain, except bone pain from acute vertebral compression fractures. · Data are inadequate to make definitive recommendations regarding combination or serial anabolic and antiresorptive drug therapies. · The treatment of osteoporosis needs to be long-term in most women. · If drug-related adverse effects occur, appropriate management strategies should be instituted. If adverse effects persist, switching to another agent may be required. · Decisions to discontinue or suspend therapy are based on the woman's risk of fracture and her response to treatment. Given the uncertainties of long-term drug safety, careful monitoring is required. Fracture risk after discontinuing therapy has not been adequately evaluated.
Institute for Clinical Systems Improvement: **Diagnosis and Treatment of Osteoporosis (2013)**[8]	· Discuss risk factors for osteoporosis and primary prevention with all patients presenting for routine health visits. · Address pharmacologic options for prevention and treatment of osteoporosis with appropriate patients at risk for or who currently have signs and symptoms of osteoporosis. · Lifestyle adjustments are universally recommended for bone health. · Adequate calcium and vitamin D intake as well as regular exercise should be discussed with patients for the prevention of osteoporosis. · Bisphosphonates are indicated for reduction of fracture (both vertebral and non-vertebral), in postmenopausal women and men, and in the setting of glucocorticoid use. · Once-yearly intravenous zoledronic acid may be given to men and women within 90 days of a hip fracture · Anabolic therapy with parathyroid hormone is indicated for patients with particularly high risk for future fracture, and data shows reduction in vertebral and non-vertebral fracture. · Nasal calcitonin is not considered third-line treatment for osteoporosis but may be useful in some populations. · Estrogen treatment is not recommended first line and should only be used in postmenopausal osteoporosis in women at significant risk that cannot take non-estrogen therapies · Consider selective estrogen receptor modulator treatment with raloxifene as it has shown vertebral risk reduction in postmenopausal osteoporosis. · Consider receptor activator of nuclear factor K-B ligand inhibitor treatment with denosumab as it has been shown to reduce the cumulative incidence

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	of new vertebral and hip fractures in postmenopausal osteoporosis. · Consider means to improve medication compliance, as poor compliance with osteoporosis medications is a large problem. Adherence is associated with significantly fewer fractures. · Follow-up central dual energy X-ray absorptiometry on the same machine as the baseline may be considered for patients on pharmacologic therapy no more than every 12 to 24 months. · Patients on glucocorticoid therapy may require testing every six to 12 months.
American College of Rheumatology: **Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis (2010)**[9]	<u>Recommendations for assessment, counseling for lifestyle modifications, and follow-up of all patients receiving glucocorticoid therapy</u> · Patients starting glucocorticoids at any dose with an anticipated duration of three or more months should receive counseling for lifestyle modification and assessment. The following should be considered: weight bearing activities, smoking cessation, avoidance of excessive alcohol intake (greater than two drinks per day), nutritional counseling on calcium and vitamin D intake, fall risk assessment, baseline dual x-ray absorptiometry, serum 25-hydroxyvitamin D level, baseline height, assessment of prevalent fragility fractures, consideration for radiographic imaging of the spine or vertebral fracture assessment for those initiating or currently receiving prednisone ≥5 mg/day or its equivalent, calcium intake (supplement plus oral intake of 1,200 to 1,500 mg/day*), and vitamin D* supplementation. · An important strategy in reducing a patient's risk is to use the smallest dose of glucocorticoid for the shortest duration possible. <u>Recommendations for low- and medium-risk postmenopausal glucocorticoid-treated women and glucocorticoid-treated men age ≥50 years</u> · Pharmacologic recommendations for postmenopausal women and men age ≥50 years starting glucocorticoid therapy with an anticipated duration of three or more months, or prevalent glucocorticoid therapy of a duration of at least three months are as follows: o Low-risk patient: § Alendronate, risedronate, or zoledronic acid for ≥7.5 mg/day prednisone. o Medium-risk patient: § Alendronate or risedronate for any dose of glucocorticoids, or zoledronic acid for ≥7.5 mg/day prednisone. · The glucocorticoid dose warranting therapeutic intervention represents the practitioner's intended average daily dose and varies according to the specific medication being considered. <u>Recommendations for high-risk postmenopausal glucocorticoid-treated women and glucocorticoid-treated men age ≥50 years</u> · Consistent with the National Osteoporosis Foundation guideline that suggests treatment when the 10-year risk of major osteoporotic fractures is ≥20%, it is recommended that these patients receive prescription osteoporosis therapy even in the absence of glucocorticoid use. · Pharmacologic recommendations for postmenopausal women and men age ≥50 years starting glucocorticoid therapy with an anticipated duration of three or more months, or prevalent glucocorticoid therapy of a duration

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	of at least three months are as follows: o High-risk patient (any anticipated dose or duration of glucocorticoids justifies initiating prescription therapy for high-risk patients): § Alendronate, risedronate, zoledronic acid, or teriparatide (for ≥5 mg/day prednisone with a duration of one month or less and for any dose of glucocorticoids with a duration greater than one month). <u>Recommendations for premenopausal women and men age <50 years</u> · Recommendations for premenopausal women and men <50 years with a history of fragility fracture are as follows: o One to three months of glucocorticoids: § Nonchildbearing potential: · Alendronate or risedronate if prednisone ≥5 mg/day, or zoledronic acid if prednisone ≥7.5 mg/day. § Childbearing potential: · Inadequate data for recommendations to be made. o Three or more months of glucocorticoids: § Nonchildbearing potential: · Alendronate, risedronate, zoledronic acid, or teriparatide for any dose. § Childbearing potential: · Alendronate, risedronate, or teriparatide if prednisone ≥7.5 mg/day. · For women of childbearing potential, drugs with shorter half-lives are recommended.

*Recommendations for calcium and vitamin D supplementation are for any dose or duration of glucocorticoids, rather than a duration for greater than three months.

<u>Conclusions</u>

Calcitonin-salmon, a calcitonin derivative, is a polypeptide containing 32 amino acids in the same linear sequence as endogenous calcitonin. Calcitonin-salmon appears to have similar actions as endogenous calcitonin but a greater potency and duration of action. The actions of calcitonin on bone and its role in normal human bone physiology are not completely understood, although calcitonin receptors have been discovered in osteoclasts and osteoblasts. In addition, it is believed that these agents cause marked transient inhibition of the ongoing bone resorptive process.[4,5]

Calcitonin-salmon is currently available as an injection, which is administered either subcutaneously or intramuscularly, or nasal spray. Miacalcin® (calcitonin-salmon) nasal spray is manufactured by chemical synthesis, and Fortical® (calcitonin-salmon) nasal spray is manufactured by recombinant deoxyribonucleic acid technology and is identical to the synthetic formulations.[4,5] Nasal calcitonin-salmon is only approved for the treatment of postmenopausal osteroporosis.[4,5] Specifically, the nasal calcitonins are for use only in postmenopausal women greater than five years postmenopause with low bone mass relative to healthy premenopausal females.[4,5] Currently, synthetic nasal calcitonin-salmon is the only calcitonin available generically.

Overall, there is a lack of substantial data demonstrating the safety and efficacy of calcitonins in FDA-approved indications, as clinical trials are typically small in size and observational in design.[11-14] For the treatment of postmenopausal osteoporosis, nasal calcitonin-salmon is associated with significant increases in bone mineral density (BMD) at the lumbar spine compared to placebo.[11-13] Furthermore, a

meta-analysis of 30 clinical trials demonstrated that calcitonins significantly decrease the risk of vertebral fractures compared to control (placebo or calcium and/or vitamin D).[14] There is also a lack of substantial head-to-head data comparing calcitonins to other established osteoporosis's treatments; however, available data supports the use of first- and second-line osteoporosis therapies over calcitonins for increasing BMD.[13] In terms of safety data, no clinically significant concerns related to the calcitonins were observed within clinical trials.[11-14]

Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options; however, the bisphosphonates are generally recognized as first-line therapy for the prevention and treatment of osteoporosis, including postmenopausal and glucocorticoid-induced osteoporosis.[1,3,6-9] Calcitonins are recognized as a potential option for the treatment of osteoporosis, and have fair quality evidence to support their use in reducing vertebral fractures.[6] They have not demonstrated a reduction in non-vertebral and hip fractures.[6] For postmenopausal osteoporosis, calcitonins are recommended as a last line therapy, and no product is recommended or preferred over another.[3,7,8]

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