



OSTEOPOROSIS DRUG DEVELOPMENT WORKSHOP

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Osteoporosis Indications Regulatory History

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Osteoporosis Definition (World Health Organization)

- **Normal:** Bone density no lower than 1 standard deviation (SD) below the mean peak bone mass (T-score > -1)
- **Low bone mass or osteopenia:** Bone density between 1.0 and 2.5 SD below the mean peak bone mass (T-score between -1 and -2.5).
- **Osteoporosis:** Bone density 2.5 SD or more below the young normal mean (T-score ≤ -2.5).

National Osteoporosis Foundation Screening Guidelines

BMD testing for:

- Postmenopausal women age 65 and older
- Postmenopausal women age 50-64, based on risk factor profile and/or fracture history
- There are no recommendations for screening all postmenopausal women younger than age 65

National Osteoporosis Foundation Treatment Guidelines

Pharmacologic treatment recommended for:

Hip or vertebral (clinical or asymptomatic) fractures

T-scores < -2.5 at the femoral neck, total hip or lumbar spine by DXA

Patients over 50 with T-scores between -1.0 and -2.5 and a 10-year hip fracture probability $> 3\%$ or a 10-year major osteoporosis-related fracture probability $> 20\%$ using the FRAX risk model



Drugs Approved for Osteoporosis

Drug	PMO Treatment	PMO Prevention	Treatment, High Risk of Fracture
estrogens	-	X	-
calcitonin	X	-	-
alendronate	X	X	-
raloxifene	X	X	-
risedronate	X	X	-
teriparatide	-	-	X
Ibandronate P.O.	X	X	-
Ibandronate I.V.	X	-	-
zoledronic acid	X	X	-
denosumab	-	-	X
risedronate delayed release	X	-	-
alendronate effervescent	X	-	-



Osteoporosis Treatment Population

Treatment Indication: Study Population

- **1994 Guidance**

- Ambulatory outpatients ≥ 5 years post menopause
- ≥ 1 vertebral fracture and/or T-score < -2
- Subjects usually ≥ 60 years of age

- **Current**

- Ambulatory outpatients
- T-score < -2.5 or
- T-score < -2 with evidence of an osteoporotic fracture
- Exclude women with multiple/severe/recent vertebral or hip fracture

Evolution of clinical trial populations

Year Started	Mean Age	Baseline LS BMD T-score	Baseline Vert. Fractures (%)
1991	71	-2.6	100
1993	69	-2.4	100
1996	69	-2.7	90
1994	69	-2.5	90
1996	69	-2.7	94
2002	73	-2.5	63
2004	72	-2.8	24

Fracture Risk Reduction across at-risk Populations

- We believe it is acceptable to extrapolate fracture risk reduction across at-risk populations
- Relative risk reductions are generally similar between lower risk and high-risk trial populations enrolled



Treatment Indication Language

Indication Language

Treatment of osteoporosis in postmenopausal women

- Demonstration of fracture reduction efficacy is required
- Encompasses primary and secondary fracture prevention in patients with osteoporosis

Evolution of the Indication Language

- Treatment of osteoporosis in postmenopausal women
- Treatment of osteoporosis in postmenopausal women at high risk of fracture, defined as history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

Evolution of the Indication Language

- High risk of fracture indication
 - For products with significant safety concerns requiring further assessment in large postmarketing clinical studies
 - Intended to be a more restrictive indication to target those patients who are most likely to derive benefit that outweighs the risks

Evolution of the Indication Language

- **We recognize there may be confusion for prescribers:**
- FDA: Treatment of postmenopausal women with osteoporosis at high risk of fracture
- EMA: Treatment of osteoporosis in postmenopausal women at increased risk of fracture



Prevention of Osteoporosis

Prevention Study Population

1994 Guidance

- Ambulatory
- ≥ 45 years of age
- Without regard to BMD

Evolved to:

Postmenopausal women with low bone mass (T-score between -1.0 and -2.5)

The Disconnect

There is a disconnect between current screening and treatment guidelines and the osteoporosis prevention indication:

- BMD screening is not recommended for patients under age 65 unless other risk factors are present
- Current osteoporosis treatment guidelines do not recommend therapy for patients with low bone mass unless there are other risk factors present

Overlap with the treatment of osteoporosis indication

Prevention Indication Language

Current Language: “...*is indicated for the prevention of postmenopausal osteoporosis.*”

The language should be refined to reflect a more targeted population for whom treatment is advised.



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Thank You