Managing Osteoporosis Patients After Long-Term Bisphosphonate Treatment
Report of a Task Force* of the American Society for Bone and Mineral Research

Task Force Co-Chairs

Robert A. Adler, MD                                     Ghada El-Hajj Fuleihan, MD, MPH, FRCP
Doug Bauer, MD, MPH                                       Beatrice Edwards, MD, FACP
Pauline Camacho, MD                                         Murray Favus, MD
Bart Clarke, MD                                               Susan Greenspan, MD
Gregory A. Clines, MD, PhD                                 Ross McKinney, Jr, MD
Juliet Compston, MD, FRCP                                    Robert Pignolo, MD, PhD
Matthew Drake, MD, PhD                                       Deborah Sellmeyer, MD

* Task Force Members vetted by ASBMR Ethics Advisory Committee
Nelson Watts Advisor to TF
Background

- Bisphosphonates (BPs) have dominated the landscape of osteoporosis therapies for the last two decades.

- Rare but Serious Adverse Events (SAEs), namely Atypical Femoral Fractures (AFF) and Osteonecrosis of the Jaw (ONJ), have raised concerns regarding the prolonged use of such drugs, topics extensively addressed by the ASBMR\textsuperscript{1,2,3}.

- The long term retention of BPs in bone, all-be-it with a differential temporal profile, and the serious AEs, led to the concept of drug holiday, to maximize benefits and minimize harms.

Background

- The ASBMR convened a multidisciplinary international task force to address the topic of “Managing Osteoporosis Patients after Long-Term Bisphosphonate Treatment”

- The Task Force initiated its work in the Fall of 2014 and this presentation reflects work in progress to-date

- The Main Recommendations of the Task Force are presented here-in in form of care pathway algorithm
Task Force Charges

- Provide guidance on duration of BP therapy in patients with postmenopausal osteoporosis, developing an algorithm that incorporates risk assessment (efficacy).
- Determine how potential harms may affect duration of therapy (safety), with a risk benefit perspective.
- Discuss how the algorithm and approach may apply to men and to glucocorticoid-induced osteoporosis.

Additional relevant points, namely risk factors for harms, resolution of benefit and harm upon BP discontinuation, monitoring on and off therapy, differential effects and costs of BPs, and alternative therapies, were also to be reviewed.

Case studies were also included to illustrate the applicability of the algorithm to realistic challenging clinical cases, where available evidence falls short of providing strong guidance and recommendations.
Members met by teleconferences and emails, in addition to 2 face-to-face meetings attended by several, but not all task force members.

Two sub-groups were formed, one charged with assessing BP effectiveness over time and the other BP safety.

TF members constructed an algorithm containing the essential findings and recommendations of the Task Force finalized by consensus.

The document is work in progress with input from all members.
BP long Term Extension Trials

FLEX
HORIZON EXTENSION
Design of Fracture Intervention Trial (FIT) Long-term Extension (FLEX) Trial

6459 Participants randomized

FIT (3-4.5 yrs)

- 3223 Assigned to receive PBO
- 3236 Assigned to receive ALN

Post-FIT (1-2 yrs)

2857 Eligible for FLEX screening

FLEX (5 yrs) PBO or ALN 5/10 mg

1099 FLEX Participants Randomized

Data available for analysis
- N=406 BMD
- N= 76 BTM

437 Assigned to PBO
662 Assigned to ALN 5 or 10 mg

McNabb B et al JBMR 2013; 28:1319
Extension Studies

FLEX

CHARACTERISTICS
N Core 6459
N extension 1099
Age $73 \pm 5.7$ yrs
Ethnicity 96% white
T-Score T hip -1.9
T-Score FN -2.2
% Prevalent Vfx 33%
% Clinical Fxs 60%
Ca/D 500 mg/250 IU

OUTCOMES
• 1 Outcome FN BMD
• 2 Outcomes BMD other sites
  BTMs (n=76)
• Exploratory Fractures
Design of HORIZON EXTENSION

7736 Participants randomized to Tmt

3876 Received PBO
3867 received ZLN 5mg (0,12,24 months)

ZLN or PBO for 3 yrs

One YR Post-Horizon

EXTENSION ZLN or PBO for 3 years

Data available for analysis
N=... BMD
N= ....BTM

1233 Participants Randomized

617 to PBO- Z3P3
616 ZLN 5 mg/YR for 3 YRS Z6
# Extension Studies

## FLEX

### CHARACTERISTICS
- **N original**: 6459
- **N extension**: 1099
- **Age**: $73 \pm 5.7$ yrs
- **Ethnicity**: 96% white
- **T-Score THip**: -1.9
- **T-Score FN**: -2.2
- **% Prevalent Vfx**: 33%
- **% Clinical Fxs**: 60%
- **Ca/D**: 500 mg/250 IU

### OUTCOMES
- 1 Outcome: FN BMD
- 2 Outcomes: BMD other sites, BTMs (n=76)
- Exploratory: Fractures

## HORIZON EXTENSION

### CHARACTERISTICS
- **N original**: 7736
- **N extension**: 1233/1040
- **Age**: $75 \pm 5.5$ yrs
- **Ethnicity**: 95% white
- **T-Score THip T**: -1.9
- **T-Score FN**: -2.55
- **Prevalent Vfx**: 60%
- **% Clinical Fxs**: ????
- **Ca/D**: +1000mg/400-1200IU

### OUTCOMES
- 1 Outcome: FN BMD
- 2 Outcomes: BMD other sites, BTMs (N=1140)
- Exploratory: Fractures, Safety
Summary of FLEX and Horizon Extension Studies

LONG TERM BP vs SWITCH to PBO

• FLEX demonstrates that continued ALN 10 yrs
  – Maintained BMD at all sites versus loss in PBO, p<0.001
  – Reduced risk of clinical vertebral fractures: RR=0.45

• HORIZON ext demonstrates that ZLN for 6 yrs
  – Maintained BMD at all sites versus loss in PBO, p<0.001
  – Reduced risk of morphometric vertebral fractures: RR=0.51

Black et al. JAMA 2006; 296:2927
Black et al. JBMR 2012; 27:240
BP long Term Extension Trials

FLEX
HORIZON EXTENSION
Risk Stratification BP vs PBO
to identify benefits of long term BP therapy
## Effect of ALN on Fracture Risk by Subgroups of Baseline FN T-Score and Prevalent Vertebral Fracture*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Non-vertebral Fractures</th>
<th>Clinical Vertebral Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo No. (%)</td>
<td>Alendronate No. (%)</td>
</tr>
<tr>
<td><strong>Baseline BMD T-score at FN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; −2.0</td>
<td>18 (10.1)</td>
<td>42 (14.9)</td>
</tr>
<tr>
<td>−2.5 to ≤−2.0</td>
<td>26 (20.6)</td>
<td>38 (20.5)</td>
</tr>
<tr>
<td>≤−2.5</td>
<td>39 (29.5)</td>
<td>43 (22.6)</td>
</tr>
<tr>
<td><strong>P value for interaction</strong>†</td>
<td>.40</td>
<td></td>
</tr>
<tr>
<td><strong>Prevalent vertebral fracture</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>48 (16.7)</td>
<td>61 (14.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>35 (23.3)</td>
<td>62 (27.7)</td>
</tr>
<tr>
<td><strong>P value for interaction</strong>‡</td>
<td>.23</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; CI, confidence interval; RR, relative risk.

*Analyses of RR and assessment of interaction were done with unadjusted proportional hazards models. Parallel analyses of morphometric vertebral fracture did not show any significant trends for alendronate efficacy among subgroups.

†Interaction between BMD as a continuous variable and treatment.

‡Interaction between prevalent vertebral fracture status and treatment.
# Effect of Continued ALN Treatment and Risk of Fracture Stratified by Baseline Presence of Vertebral Fracture and FN T-Score

<table>
<thead>
<tr>
<th>Femoral neck T-score at FLEX baseline</th>
<th>Non-vertebral</th>
<th>Morphometric vertebral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>PBO No. (%)(^a)</td>
</tr>
<tr>
<td>No VF at FLEX baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2&lt; FLEX FN T-score</td>
<td>333</td>
<td>14 (10.8)</td>
</tr>
<tr>
<td>-2.5&lt;FLEX FN T-score ≤ -2</td>
<td>203</td>
<td>13 (15.9)</td>
</tr>
<tr>
<td>FLEX FN T-score ≤2.5</td>
<td>184</td>
<td>21 (28.0)</td>
</tr>
<tr>
<td>P value for interaction(e)</td>
<td></td>
<td>.019</td>
</tr>
<tr>
<td>Vertebral fracture at FLEX baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2&lt; FLEX FN T-score</td>
<td>128</td>
<td>4 (8.2)</td>
</tr>
<tr>
<td>2.5&lt;FLEX FN T-score2</td>
<td>108</td>
<td>13 (29.5)</td>
</tr>
<tr>
<td>FLEX FN T-score ≤2.5</td>
<td>138</td>
<td>18 (31.6)</td>
</tr>
<tr>
<td>P value for interaction(e)</td>
<td></td>
<td>.60</td>
</tr>
</tbody>
</table>

\(^a\)Number of participants with at least one fracture in the FLEX placebo group.

\(^b\)Number of participants with at least one fracture in the FLEX ALN group (5 and 10 mg/day combined).

\(^c\)Relative hazard estimated with Cox proportional hazard models for time to first fracture.

\(^d\)Odds ratio estimated with logistic regression models.

\(^e\)p Values for tests of interaction. Relative risks were tested for multiplicative interaction with FN T-score as a continuous variable. Appendix IV-B

Schwartz et al. JBMR 2010; 25(5):976–982
Stratification of TH BMD: Incident Morphometric Vertebral Fracture Rates

- **TH BMD ≤ -2.5**
  - 14.3% (16/112)
  - OR: 0.26 (95% CI: 0.08, 0.69)
  - *P* = 0.0113
  - NNT = 9.9

- **TH BMD > -2.5**
  - 3.8% (14/373)
  - OR: 0.68 (95% CI: 0.28, 1.58)
  - *P* = 0.3793
  - NNT = 86.2

**Z3P3**

**Z6**

Treatment subgroup interactions not significant

BMD, bone mineral density; CI, confidence interval; TH, total hip; NNT, number needed to treat; OR, odds ratio

Cosman F et al. JCEM 2014. in press
Stratification of FN BMD: Incident Morphometric Vertebral Fracture Rates

<table>
<thead>
<tr>
<th>Proportion of Patients (%)</th>
<th>Z3P3</th>
<th>Z6</th>
</tr>
</thead>
<tbody>
<tr>
<td>FN BMD ≤ -2.5</td>
<td>9.2 % (23/250)</td>
<td>3.5 % (9/257)</td>
</tr>
<tr>
<td></td>
<td>NNT= 18</td>
<td>NNT= 18</td>
</tr>
<tr>
<td>FN BMD &gt; -2.5</td>
<td>3.0 % (7/235)</td>
<td>2.4 % (5/210)</td>
</tr>
</tbody>
</table>

OR: 0.36 (95% CI: 0.15, 0.77) P = 0.01
OR: 0.79 (95% CI: 0.23, 2.53) P = 0.70

Treatment subgroup interactions not significant

BMD, bone mineral density; CI, confidence interval; FN, femoral neck; NNT, number needed to treat; OR, odds ratio

Cosman F et al. JCEM 2014. in press
Stratification by Incident Vertebral Fracture During Core Study: Incident Morphometric Vertebral Fracture Rates

- **Incident vertebra fracture During Core**
  - **Z3P3**
    - 25% (4/16)
    - $P = 0.12$
    - NNT = 4
  - **Z6**
    - NA (0/11)
  - Treatment subgroup interactions not significant

- **Non Incident vertebra fracture During Core**
  - **Z3P3**
    - 5.6% (26/467)
    - OR: 0.46
      - (95% CI: 0.22, 0.90)
      - $P = 0.03$
      - NNT = 34
  - **Z6**
    - 2.6% (12/454)

CI, confidence interval; NNT, number needed to treat; OR, odds ratio
Differences between Z6 and Z3P3 groups were analyzed during Fisher’s exact test for categorical variables

Cosman F et al. JCEM 2014. in press
Summary of FLEX and Horizon Extension Studies

LONG TERM BP vs SWITCH to PBO

• FLEX demonstrates that continued ALN 10 yrs
  – Reduceda risk of clinical fractures in subgroup analyses 1 by prevalent fracture status or BMD subgroups: in those with FN BMD T-score > -2.5 and ≤-2 benefited most RR=0.22[0.05-0.74]¹
  – Reduced risk of non-vertebral fractures in subgroup analyses 2 by fracture status and BMD subgroups: if FN BMD T-score ≤ -2.5, RR=0.50 [0.26-0.96]²

• HORIZON ext demonstrates that ZLN for 6 yrs reduced risk of morphometric vertebral fractures ³
  – If Total hip T-score ≤ -2.5, RR=0.26 [0.08-0.69] but no treatment subgroup interaction
  – If FN BMD T-score ≤ -2.5, RR= 0.36 [0.15-0.77], but no treatment subgroup interaction

1. Black et al. JBMR 2006; 296: 2927
2. Schwartz A et al JBMR 2010; 25:976
3. Cosman F et al JCEM 2014 in press
BP long Term Extension Trials

FLEX
HORIZON EXTENSION
Risk Stratification in Discontinuation groups
To identify high risk patients who may benefit for long term BP therapy
Proportion of Women With Any Clinical Fracture After ALN Discontinuation

A. By tertile of hip bone mineral density (BMD) at Fracture Intervention Trial Long-term Extension (FLEX) baseline. *P* for trend < 0.01 for total hip BMD and for femoral neck BMD. B. By tertile of bone turnover marker at FLEX baseline. *P* for trend = .18 for urinary type 1 collagen cross-linked N-telopeptide to creatinine concentration ratio (NTX/Cr) and .40 for serum bone-specific alkaline phosphatase (BAP). C. By tertile of 1-year percent change in hip BMD. *P* for trend = .96 for total hip BMD and .81 for femoral neck BMD. D. By tertile of 1-year percent change in bone turnover marker. *P* for trend = .91 for NTX/Cr and .70 for BAP.
## Variables Measured at FLEX Baseline

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics</th>
<th>Risk of Fracture, Relative Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 5-y increase, y</td>
<td>1.54 (1.26-1.85)</td>
</tr>
<tr>
<td>BMI, per SD increase</td>
<td>1.10 (0.87-1.38)</td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td>1.11 (0.71-1.75)</td>
</tr>
<tr>
<td>Previous non-spine fracture</td>
<td>1.24 (0.64-2.40)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMD, lowest tertile vs other 2, T-score</th>
<th>Risk of Fracture, Relative Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip</td>
<td>1.87 (1.20-2.92)</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>2.17 (1.38-3.41)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BTMs, highest tertile vs other 2</th>
<th>Risk of Fracture, Relative Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTX/Cr, nmol/mmol</td>
<td>1.33 (0.84-2.10)</td>
</tr>
<tr>
<td>BAP, ng/mL</td>
<td>1.39 (0.89-2.17)</td>
</tr>
</tbody>
</table>

Abbreviations: BAP, bone-specific alkaline phosphatase; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FLEX, Fracture Intervention Trial Long-term Extension; NTX/Cr, type 1 collagen cross-linked N-telopeptide to creatinine concentration ratio.

\(^a\) With the exception of age, each variable was examined in a separate age-adjusted model.

\(^b\) Any non-spine or clinical vertebral fracture occurring after the 1-year visit.
## Predictors of Morphometric Vertebral Fracture in Discontinuation Group (Z3P3) During Extension Study (univariable models)

<table>
<thead>
<tr>
<th>Factors at Extension Baseline</th>
<th>Odd Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>1.33 (0.62, 2.86)</td>
<td>0.461</td>
</tr>
<tr>
<td><strong>FN T-score as categorical (~55% of population)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ -2.5</td>
<td>3.32 (1.37, 8.05)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>TH T-score as categorical (~25% of population)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ -2.5</td>
<td>3.99 (1.79, 8.92)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

| Factors During Core Trial                                       |                      |         |
| Incident Vertebral Fracture                                     | Yes                  | 4.75 (1.35, 16.77) | 0.015   |

Cosman F et al. JCEM 2014. in press
Predictors of Non-Vertebral Fracture in Discontinuation Group (Z3P3) During Extension Study (univariable models)

<table>
<thead>
<tr>
<th>Factors at Extension Baseline</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 75 years</td>
<td>1.32 (0.73, 2.39)</td>
</tr>
<tr>
<td>TH T-score as continuous variable</td>
<td>per -1</td>
<td>1.72 (1.15, 2.56)</td>
</tr>
<tr>
<td>Prevalent Vertebral Fracture</td>
<td>Yes</td>
<td>2.96 (1.38, 6.34)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factors During Core Trial</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident Non-Vertebral Fracture</td>
<td>Yes</td>
<td>2.54 (1.21, 5.33)</td>
</tr>
</tbody>
</table>

Cosman F et al. JCEM 2014. in press
### Absolute Risk of Morphometric Vertebral Fracture in Subgroups Defined by Combining Risk Predictors by Increasing Level of Risk in Z3P3 Subgroups and in Same Z6 Subgroups with NNT to Prevent 1 Morphometric Vertebral Fracture

| At Extension Baseline | During Core | | | |
|----------------------|------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| FN T-score ≤-2.5     | TH T-score ≤-2.5 | Prevalent Vertebral Fracture | Incident Vertebral Fracture | Incident Non-vertebral Fracture | % (N) | Z3P3 % fx (n/N) | Z6 % fx (n/N) | NNT |
| No                   | No         | No              | No              | No              | 16.1 % (152) | 2.8 % (2/72)    | 1.3 % (1/80)    | 65 |
| Yes                  | No         | No              | No              | No              | 12.7 % (120) | 3.1 % (2/64)    | 1.8 % (1/56)    | 75 |
| No                   | No         | Yes             | No              | No              | 25.3 % (239) | 3.8 % (5/133)   | 2.8 % (3/106)   | 108 |

In Horizon Ext risk of morphometric fracture is low over three years, less than 4% if only one risk factor, Hip T-score ≤ -2.5 of prevalent vertebral fracture, and NNT 65-108

Cosman F et al. JCEM 2014. in press
### Absolute Risk of Morphometric Vertebral Fracture in Subgroups Defined by Combining Risk Predictors by Increasing Level of Risk in Z3P3 Subgroups and in Same Z6 Subgroups with NNT to Prevent 1 Morphometric Vertebral Fracture

<table>
<thead>
<tr>
<th>At Extension Baseline</th>
<th>During Core</th>
<th>% (N)</th>
<th>Z3P3 % fx (n/N)</th>
<th>Z6 % fx (n/N)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FN T-score ≤ -2.5</td>
<td>TH T-score ≤ -2.5</td>
<td>Prevalent Vertebral Fracture</td>
<td>Incident Vertebral Fracture</td>
<td>Incident Non-vertebral Fracture</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>14.7 % (139)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>7.1 % (67)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>12.2 % (115)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>1.2 % (11)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>1.2 % (11)</td>
</tr>
</tbody>
</table>
Summary of FLEX and Horizon Extension Studies
Off Therapy

- As age increases (discrete or continuous entry) or BMD (T-hip or FN) decreases (categorical or with cut-off -2 vs -2.5) fracture risk increases.

- Incident vertebral fracture (during core study) increases risk of vertebral fractures after ZLN D/C.

- Incident non-vertebral fracture (during core study) increases risk of non-vertebral fractures after ZLN D/C.

- As number of RF increases FX risk increases off therapy and recent incident fractures (within 3 years) of therapy discontinuation decreases risk the most.
Safety Figure

- Awaiting final version with corrections as per Tel conf
  – Next slide has what we received Aug 4 from Beatrice.
Benefits and Risks Associated with Bisphosphonate Use

The risk of BP associated adverse events is compared to everyday risks such as being hit by a car or murder. AFF = atypical femur fracture; ONJ = osteonecrosis of the jaw; BP = bisphosphonates

Dell JBMR 2012; Cauley Nature Reviews 2014; CDC 2013; CDC 2014
“SIDE BENEFITS” OF BP THERAPY

- Decreased risk of breast cancer, in many studies\(^1-6\), but NOT FIT and HORIZON\(^7\)
- Decreased risk of colorectal cancer\(^7\)
- Decreased risk of stroke\(^8\)
- Decreased risk of MI\(^9\)
- Reduced risk of gastric cancer\(^10\)
- Decreased overall mortality\(^11, 12, 13\)

2. Dreyfuss JH. *CA Cancer* 2010; 60:343.
7. Hue TF *JAMA* 2014 [Epub ahead of print]*
10. Abrahamsen B et al. *J Bone Miner Res* 2012;27:679

*Red font used for RCTs*
# Osteoporosis Drugs: Approved Indications 2014: North America

<table>
<thead>
<tr>
<th>Anti-Remodeling Agents</th>
<th>Postmenopausal Osteoporosis</th>
<th>Men</th>
<th>GIO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevention</td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-Remodeling Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Risedronate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Denosumab</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Estrogen</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Conjugated estrogen/basodoxifene</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>-</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td><strong>Anabolic Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

© M MClung 2014

From Prescribing Information of each agent
## Osteoporosis Drugs: Approved Indications 2014: Europe

<table>
<thead>
<tr>
<th>✓ = Approved</th>
<th>Postmenopausal Osteoporosis</th>
<th>Men</th>
<th>GIO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-REMODELING AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Risedronate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lasofoxifene</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Basodoxifene</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Denosumab</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td><strong>ANABOLIC AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

*Courtesy M McClung 2014 From Prescribing Information of each agent*
Algorithm for Management of Postmenopausal Women on Long Term Bisphosphonate Therapy

Post-menopausal women treated with oral (≥ 5yrs) or IV (≥ 3 yrs) BPs

≥ 3-5 years but <10 years

Hip, spine, or multiple other osteoporotic fractures before or during therapy

Yes

Continue BP (1), or change to alternative anti-fracture therapy (2)
Reassess every 2-3 years

No

Hip BMD T-Score ≤ -2.5 (3)

or

High fracture risk (4)

Yes

Consider Drug Holiday
Reassess every 2-3 years (5)

No

Continue BP for up to 10 yr (1), or change to alternative anti-fracture therapy (2)
Reassess every 2-3 years (5)

(1) Continue BP therapy with oral therapy for up to 10 years or intravenous therapy for up to 6 years. For patients who fracture on therapy, assess adherence and rule out secondary causes of osteoporosis. Management in high risk patients after 10 years of BP therapy is discussed in the text.

(2) The benefits of switching to an alternative anti-fracture therapy after prolonged bisphosphonate treatment have not been adequately studied.

(3) Based on FLEX study (American white women), may not apply to other populations.

(4) High fracture risk: defined by older age (70-75 yrs), other strong risk factors for fracture, or FRAX fracture risk score that is above country specific thresholds. The use of FRAX in patients on therapy was only assessed in the Manitoba observational cohort (Leslie JBMR 2012).

(5) Reassessment includes clinical evaluation, risk assessment including risk factors, and may include bone density measurement by DXA. DXA monitoring interval should be based upon changes that are detectable and clinically significant. Reassessment may be necessary at less than 2 years in patients with a new fracture, or in light of anticipated accelerated bone loss (e.g. institution of aromatase inhibitor or glucocorticoid therapy).
Algorithm for Management of Postmenopausal Women on Long Term Bisphosphonate Therapy

1. Post-menopausal women treated with oral (≥ 5yrs) or IV (≥ 3 yrs) BPs
   - ≥ 3-5 years but <10 years

2. Hip, spine, or multiple other osteoporotic fractures before or during therapy
   - Yes: Continue BP, or change to alternative anti-fracture therapy. Reassess every 2-3 years.
   - No: Hip BMD T-Score ≤ -2.5 or High fracture risk
     - Yes: Consider Drug Holiday. Reassess every 2-3 years.
     - No: Continue BP for up to 10 yr, or change to alternative anti-fracture therapy. Reassess every 2-3 years.
Algorithm for Management of Postmenopausal Women on Long Term Bisphosphonate Therapy

Post-menopausal women treated with oral (≥ 5yrs) or IV (≥ 3 yrs) BPs
≥ 3-5 years but <10 years

Hip, spine, or multiple other osteoporotic fractures before or during therapy

Yes

Continue BP (1), or change to alternative anti-fracture therapy (2)
Reassess every 2-3 years

(1) Continue BP therapy with oral therapy for up to 10 years or intravenous therapy for up to 6 years. For patients who fracture on therapy, assess adherence and rule out secondary causes of osteoporosis. Management in high risk patients after 10 years of BP therapy is discussed in the text.

(2) The benefits of switching to an alternative anti-fracture therapy after prolonged bisphosphonate treatment have not been adequately studied.
Algorithm for Management of **Postmenopausal Women on Long Term Bisphosphonate Therapy**

- **Post-menopausal women treated with oral (≥ 5yrs) or IV (≥ 3 yrs) BPs**
  - ≥ 3-5 years but <10 years

  → Hip, spine, or multiple other osteoporotic fractures before or during therapy

  → **No**

  **Hip BMD T-Score ≤ -2.5 (3)** or **High fracture risk (4)**

---

- **(3)** Based on FLEX and HORIZON studies (Mostly white women), may not apply to other populations.

- **(4)** High fracture risk: defined by older age (70-75 yrs), other strong risk factors for fracture, or FRAX fracture risk score that is above country specific thresholds. The use of FRAX in patients on therapy was only assessed in the Manitoba observational cohort (Leslie JBMR 2012).
Algorithm for Management of Postmenopausal Women on Long Term Bisphosphonate Therapy

- (1) Continue BP therapy with oral therapy for up to 10 years or intravenous therapy for up to 6 years. For patients who fracture on therapy, assess adherence and rule out secondary causes of osteoporosis. Management in high risk patients after 10 years of BP therapy is discussed in the text.

- (2) The benefits of switching to an alternative anti-fracture therapy after prolonged bisphosphonate treatment have not been adequately studied.

- (5) Reassessment includes clinical evaluation, risk assessment including risk factors, and may include bone density measurement by DXA. DXA monitoring interval should be based upon changes that are detectable and clinically significant. Reassessment may be necessary at less than 2 years in patients with a new fracture, or in light of anticipated accelerated bone loss (e.g. institution of aromatase inhibitor or glucocorticoid therapy).
Algorithm for Management of Postmenopausal Women on Long Term Bisphosphonate Therapy

- Reassessment includes clinical evaluation, risk assessment including risk factors, and may include bone density measurement by DXA. DXA monitoring interval should be based upon changes that are detectable and clinically significant. Reassessment may be necessary at less than 2 years in patients with a new fracture, or in light of anticipated accelerated bone loss (e.g. institution of aromatase inhibitor or glucocorticoid therapy).

ASBMR Long Term BP Task Force

**Hip BMD T-Score ≤ -2.5** (3)

or

**High fracture risk** (4)

No

**Consider Drug Holiday**

**Reassess every 2-3 years** (5)
Limitations of Evidence and of Algorithm

- Low Power: small sample size and number of fractures, post-hoc exploratory nature for many analyses, and lack of correction for multiple comparisons in extension studies.

- Findings are not consistent across FLEX and HORIZON Extension: reduction in clinical vertebral Fxs (ALN) and morphometric Vfxs (ZLN) with therapy continuation

- Efficacy of prolonged therapy is for 2 BPs only ALN and ZLN, and no other BPs

- Evidence for variables to monitor off therapy is lacking
Limitations of Algorithm

- Data to assess risk stratification by incident fractures after BP discontinuation is limited, and includes age, FN (FLEX, Horizon) and T-Hip (Horizon) T-score (which were predictors as categorical and continuous variables).

- No evidence for risk stratification by hip T-score ≤ -2.5 in non-Caucasian subjects.

- There is no good evidence validating use of FRAX on therapy with long term BP.

- There are no trials demonstrating that after a drug holiday, re-institution of BP treatment, or switching to alternative therapies, results in fewer fractures.
Consultants

**Australia**
Peter Ebeling, MD, FRCP

**Canada**
Aliya Khan, MD, FRCPC, FACP
William Leslie, MD, MSc, FRCPC

**China**
Edith Lau, MD

**India**
Ambrish Mithal, MD, DM

**Japan**
Akira Itabashi, MD

**United Kingdom**
Richard Eastell, MD., FRCP

**USA**
Dennis Black, PhD
Michael McClung, MD