

FDA Public Workshop
Osteoporosis Drug Development
04 November 2015

Session I: Osteoporosis Treatment
and Prevention: Indication Language
and Target Population

Industry Perspective

Companies Represented

- Represents the position of an industry working group of participating sponsors, participating companies were (in alphabetical order):
 - Amgen, Inc.
 - Eli Lilly and Co.
 - Merck Sharp & Dohme Corp.
 - Radius Health, Inc.
 - Sermonix Pharmaceuticals, LLC
 - Tarsa Therapeutics, Inc.

Views on Indication Statement Treatment

- The current two-tiered indication structure, which separates “treatment of osteoporosis” and “treatment of osteoporosis at high risk for fracture” in postmenopausal women is seen as potentially confusing
- Among the industry group, there was consensus favoring a single treatment indication statement – an example could be:

TRADEMARK is indicated for the treatment of
osteoporosis [disease] in postmenopausal women
[population]

Views on Indication Statement Treatment

- Examples on how to arrive at a clinical diagnosis of osteoporosis (rather than specific diagnostic criteria) could be given as guidance for physicians within the prescribing information but should not be included in the indication statement as the precise definition of osteoporosis is likely to be constantly evolving.
- Examples might include:
 - patients with prevalent fractures after the age of 50
 - patients with a BMD T-score of -2.5 SD or below at either the hip or spine
 - evidence of increased risk for fracture in established risk assessment tools
- There were different industry views on exact placement of such information in the prescribing information.

Views on Indication Statement Treatment

- Following the statement of disease and target population, the Indication might include a second part which articulates the demonstrated benefit (either at the end of the initial sentence or as a second sentence per the example below).
- Risk reduction at specific anatomical sites, if demonstrated in the pivotal clinical trials should be retained to describe the efficacy that has been demonstrated with the product. An example could be:

TRADEMARK reduces the incidence of fractures (name specific sites where fracture reduction has been demonstrated)[claim]

Views on Indication Statement Treatment - Enrolled population

- Too much specificity in describing the disease state in the indication statement should be avoided, as the evidence points to the possibility to extrapolate results across different levels of disease severity.
- In general, the enrolled population in clinical trials should be consistent with the clinical definition of osteoporosis (examples are given on the previous slide), which would ensure alignment with the indication statement.

Views on Indication Statement Treatment-Enrolled population

Effects on fracture risk of currently available treatment are generalizable across populations with differing degrees of fracture risk

- Evidence across clinical trials suggests that the effect of drugs on vertebral fracture incidence can be extended across a gradient of risk.
 - An overall consistent reduction in vertebral fracture risk has been observed in patients at the higher and the lower end of the risk spectrum of postmenopausal osteoporosis with various drugs and/or mechanisms of action (Boonen, JCEM, 2011, Eastell, JCEM, 2009).

Views on Indication Statement Treatment-Enrolled population

- Non-vertebral fracture efficacy seems somewhat more variable.
 - However, as non-vertebral fractures have generally been a secondary endpoint, most trials were not designed to analyze the efficacy within subgroups (e.g., BMD T-score) on non-vertebral fractures with adequate statistical power.
- When the treatment effect to reduce major osteoporotic fractures was assessed over a broad range of baseline risk (e.g. as determined by FRAX) for a number of drugs, general efficacy was usually observed across the population (McCloskey, JBMR, 2012; Harvey, OI, 2014)

Views on Indication Statement Prevention

- More than half of non-vertebral fractures occur in postmenopausal women with BMD T-score values higher than -2.5 (Siris et al, JAMA 2001). Siris reported a fracture rate in postmenopausal women with BMD T-scores between -1 and -2.5 that was 1.8-fold higher than the rate in women with BMD T-scores > -1 . There appears to be value in providing treatment to prevent bone loss and progressive increase in fracture risk in postmenopausal women with low BMD, even if they don't fulfil the current operational definition of osteoporosis
- This could be expressed in an indication statements as follows:
Use of TRADEMARK for the prevention of osteoporosis in postmenopausal women with low bone mass and additional risk factor(s) for fracture (e.g. progressive bone loss)

Views on Indication Statement Prevention

- As some of the drugs which might be used for prevention may also convey other benefits, a statement like the following might be added:

Other postmenopausal symptoms and concerns may also be taken into consideration when making treatment and benefit/risk decisions.

Summary

- **Treatment of osteoporosis:**
 - Simple indication statement preferred
 - Enrolled population in clinical trials should be generally consistent with the clinical definition of osteoporosis
- **Prevention of osteoporosis:**
 - Patients with low bone mass may benefit from pharmacological intervention, when additional risk factors convey an increased fracture risk