

For Osteoporosis in Postmenopausal Women

Summary

Drugs Under Review

ICER's report reviewed evidence on the clinical effectiveness and value of two drugs for osteoporosis: teriparatide (Forteo™, Eli Lilly and Co.) and abaloparatide (Tymlos™, Radius Health, Inc.). Both drugs are anabolic agents – drugs that increase formation of new bone.

Key Findings

- Compared to placebo, anabolic agents reduce rates of vertebral and non-vertebral fractures and produced similar rates of adverse events. Evidence provides moderate certainty of a small to substantial net health benefit.
- Evidence is promising but inconclusive on the net health benefit of anabolic agents compared to zoledronic acid, another treatment for osteoporosis.
- Evidence is insufficient to distinguish between the two anabolic agents.
- To understand the full impact of anabolic agents, studies are needed comparing the drugs to existing treatments, and more research is needed on important outcomes, including hip fractures and patient-centered outcomes.

The report was subject to public deliberation during a public meeting of the California Technology Assessment Forum.

Value-Based Price Benchmarks

ICER's report found that prices of the drugs do not align with their potential benefits, and would need to be substantially lowered.

**Teriparatide: \$330–\$420 per pen,
an 86% to 89% discount from current list price**

**Abaloparatide: \$520–\$665 per pen,
a 59% to 68% discount from current list price**

Potential Short-Term Budget Impact

We did not assess the budget impact of teriparatide because it has been available for over a decade. At list price and below, the potential budget impact of abaloparatide is unlikely to generate access or affordability alerts, which would occur in cases where short-term costs may create strains on health care budgets.

For Osteoporosis in Postmenopausal Women

Report-at-a-Glance

What is Osteoporosis?

Osteoporosis is the weakening of bones caused by a decrease in density and quality. Bone is constantly being broken down (resorption) and rebuilt. By mid-life, the body begins to break down bone faster than it can be rebuilt. As a result, osteoporosis becomes more common as people age. The condition is currently estimated to affect approximately 10 million Americans, although this may be an underestimate.

People with osteoporosis do not have symptoms until they break a bone. Broken bones that occur after minimal trauma, such as a fall from standing height or lower, are known as fragility fractures. Approximately half of women and one quarter of men will have at least one fragility fracture due to osteoporosis during their lifetimes.

Treating Osteoporosis

The goal of treatment is to prevent the fragility fractures associated with osteoporosis. These fractures happen most commonly at the hip, spine, and wrist. Osteoporosis is typically treated with a group of drugs known as bisphosphonates. Alendronate (Fosamax®, Merck) is an oral bisphosphonate, and zoledronic acid (Reclast®, Novartis) is an intravenous bisphosphonate. These drugs are “anti-resorptive” agents, and they work by slowing the breakdown of bones.

Drugs Under Review

There are several newer drugs, known as anabolic agents, that treat osteoporosis by increasing the building of new bone. ICER’s review includes two anabolic therapies. Both therapies require a daily injection and come in a pen device:

WAC* prices	Number of pens needed per year
Teriparatide (Forteo™, Eli Lilly and Co.)	
\$3,000 per pen	About 13
Abaloparatide (Tymlos™, Radius Health, Inc.)	
\$1,625 per pen	About 12

* Wholesale acquisition cost

Teriparatide must be refrigerated at all times. Abaloparatide needs to be refrigerated until the first dose.

Romosozumab (Amgen and UCB, Inc.), a third anabolic agent, was initially included in ICER’s review, but the FDA had delayed its decision on the drug at the time of the report and public meeting. A summary of key trials related to romosozumab is included in the full report.

How strong is the evidence that anabolic agents improve patient outcomes?

Clinical Outcomes

Vertebral and Non-vertebral fragility fractures

Key trials of teriparatide, abaloparatide, and zoledronic acid all reported a significant reduction in vertebral fractures and non-vertebral fragility fractures versus placebo. Results of ICER's network meta-analysis confirmed these findings. Evidence was inadequate to distinguish the anabolic agents from each other or from zoledronic acid.



Hip Fractures

The incidence of hip fractures in studies of anabolic agents was low. Relative risk estimates for abaloparatide and teriparatide were not reported. Some observational studies suggest that teriparatide reduces hip fractures.

Bone Mineral Density (BMD)

Change in BMD is often used as a surrogate marker in preliminary studies of drugs to prevent osteoporotic fractures. Evidence showed increases of BMD of the lumbar spine, total hip, and femoral neck among the anabolic agents and zoledronic acid.



While increases were observed, BMD is an imperfect predictor of fracture prevention, so it is difficult to draw firm conclusions from these results.

Risks

Teriparatide and abaloparatide carry a theoretical risk for bone cancer (osteosarcoma). However, this concern arose in animal studies and has not been observed in human studies to date. There were no differences in serious adverse events between the drugs and placebo in the randomized trials.

Bisphosphonates are thought to cause two rare but serious side effects: atypical fractures of the femur (the long bone in the thigh) and osteonecrosis ("death of bone") of the jaw. These conditions are painful and require extensive additional treatment.

However, the risk of hip fracture (the most serious fragility fracture) in untreated patients is higher than the risks of either of these rare adverse events. It is estimated that for every atypical femoral fracture that occurs due to bisphosphonate therapy, 110 hip fractures are prevented; even greater numbers of vertebral and other fractures are prevented. Because of this, doctors are comfortable treating patients with bisphosphonates.

How strong is the evidence that anabolic agents improve patient outcomes? (continued)

Sources of Uncertainty

Limited data: Available trials of anabolics were relatively small, and active treatment continued for only one to two years because of the long-term safety concerns related to bone cancer. Additionally, a low number of hip fractures observed in the trials made it difficult to determine how well the drugs reduce hip fractures. A lack of head-to-head data increased the uncertainty in between- and within-class comparisons.

Treatment sequence: Evidence suggests that bone density begins to decrease quickly when anabolic drugs are stopped, so they must be followed by treatment with a drug that decreases bone breakdown. Evidence also suggests that the anabolic drugs may not work as well when used after patients have been treated with bisphosphonates. The optimal sequence of drugs and the appropriate length of treatment are uncertain.

Patient-centered outcomes: The outcomes of greatest interest to patients are maintenance of independence and prevention of disability. These and other patient-centered outcomes were not reported in the clinical trials.

ICER Evidence Ratings

For postmenopausal women with osteoporosis at high risk for fracture:

- Evidence provides moderate certainty of a small or substantial net health benefit of anabolic agents compared to no therapy, with high certainty of at least a small net health benefit.
- Evidence is promising but inconclusive on the net health benefit of anabolic agents compared to zoledronic acid.
- Evidence is insufficient to distinguish between the two anabolic agents.

What is a fair price for anabolic agents based on their value to patients and the health care system?

Long-Term Cost-Effectiveness at Net Price

The cost-effectiveness of treatment with each anabolic agent followed by zoledronic acid compared to treatment with zoledronic acid alone in postmenopausal women with osteoporosis at high risk for fragility fractures was calculated to be above \$150,000 per quality-adjusted life-year (QALY), a level that is commonly cited as the upper threshold for cost-effective treatments.

- Teriparatide: \$942,000 per QALY
- Abaloparatide: \$334,000 per QALY

To calculate these results, we assumed a 38% and 27% discount off the list prices of teriparatide and abaloparatide, respectively. These results did not significantly change over a wide range of sensitivity and scenario analyses.

ICER's Value-Based Price Benchmarks

Drug name	WAC per pen	Net price per pen*	Value-based price benchmarks	Discount from WAC to reach benchmark threshold	Average net price within benchmark range?
Teriparatide	\$3,000	\$1,870 [†]	\$330–\$420	86% to 89%	X
Abaloparatide	\$1,625	\$1,190 [‡]	\$520–\$665	59% to 68%	X

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Net price is the estimated price after discounts and rebates from WAC

[†] Price per pen including 38% discount based on data from SSR Health

[‡] Price per pen based on announced list price and assumed 27% discount, the average industry-wide discount for branded drugs

To fall within ICER's threshold value range of \$100,000 to \$150,000 per QALY, both agents would require discounts that are greater than the current discounts from WAC.

Potential Short-Term Budget Impact at List Price

We did not assess the budget impact of teriparatide because it has been available for over a decade. At list price and below, the potential budget impact of abaloparatide is unlikely to generate access or affordability alerts.

Public Deliberation and Evidence Votes

California Technology Assessment Forum Votes

The California Technology Assessment Forum (CTAF) deliberated on key questions raised by ICER’s report at a public meeting on June 30, 2017. The results of the votes are presented below. More detail on the voting results is provided in the [full report](#).

1. For postmenopausal women with osteoporosis and a high risk* of fracture, is the evidence adequate to demonstrate that the net health benefit of treatment with teriparatide (Forteo®, Eli Lilly and Co.), is greater than that of treatment with zoledronic acid?

Yes: 2 votes	No: 13 votes
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2. For postmenopausal women with osteoporosis and a high risk* of fracture, is the evidence adequate to demonstrate that the net health benefit of treatment with abaloparatide (Tymlos™, Radius Health Inc.), is greater than that of treatment with zoledronic acid?

Yes: 2 votes	No: 13 votes
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3. For postmenopausal women with osteoporosis and a high risk* of fracture, is the evidence adequate to distinguish between the net health benefit of teriparatide and abaloparatide?

Yes: 2 votes	No: 13 votes
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4. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with teriparatide followed by zoledronic acid versus treatment with zoledronic acid alone for postmenopausal women with osteoporosis at high risk* for fracture?

Low: 13 votes	Intermediate: 2 votes	High: 0 votes
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5. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with abaloparatide followed by zoledronic acid versus treatment with zoledronic acid alone for postmenopausal women with osteoporosis at high risk* for fracture?

Low: 13 votes	Intermediate: 2 votes	High: 0 votes
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*Per the US Food and Drug Administration (FDA) labeled indication for the anabolic agents, high risk for fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or an intolerance to or failure of other available osteoporosis therapy.

Key Policy Implications

The CTAF Panel engaged in a moderated discussion with a policy roundtable of subject-matter experts about how best to apply evidence on anabolic therapies for osteoporosis in policy and practice. The roundtable included a patient, clinical experts, drug manufacturer representatives, and private payer representatives. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. Below are the top-line policy implications; for more information please see the [full report](#).

For Manufacturers

- Reduce the prices of anabolic agents to align with the clinical benefits they bring to patients.
- Abstain from direct to consumer advertising and detailing to primary care providers, who may be less experienced in identifying patients at high fracture risk.
- Include broader patient groups, including those at highest risk for fracture, in randomized trials.

For Payers

- Design coverage policies with a broad set of criteria by which to determine whether an anabolic therapy may be a more appropriate first choice than intensive anti-resorptive therapy.
- Create a prior authorization process for anabolic therapies that is clear and efficient for providers.
- If the prices of anabolic agents are reduced, ease access restrictions.

For Patient Groups

- Demand the inclusion of patient-centered outcomes in clinical trials.
- Continue to promote lifestyle changes that protect against osteoporosis.

For Specialty Societies

- Develop clear guidelines for use of anabolic agents that define the level of risk that would warrant initial treatment with an anabolic agent.

For Regulatory Agencies

- Promote hip fracture as the most important outcome in pivotal clinical trials.
- Require that pivotal trials in high-risk patients include an active comparator

For Researchers

- Develop risk assessment tools that identify patients with osteoporosis with extremely high risk for fracture who warrant treatment with therapies other than bisphosphonates.

Conclusion

Comparative Clinical Effectiveness

Available evidence demonstrates with high certainty that the two anabolic agents reduce vertebral and non-vertebral fractures compared to no therapy. However, there is insufficient evidence to distinguish the anabolic agents from one another or from zoledronic acid.

Comparative Value

At both list and discounted prices, the anabolic agents exceeded commonly-cited benchmarks for cost-effective treatments, meaning that their prices are not aligned with the benefits to patients. The discounts required to achieve good value are greater than estimated current discounts from list price.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).