

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Abaloparatide for treating osteoporosis after menopause

1 Recommendations

- 1.1 Abaloparatide is recommended as an option for treating osteoporosis after menopause in women, trans men and non-binary people, only if they have a very high risk of fracture (see [section 3.2](#)). It is only recommended if the company provides it according to the commercial arrangement (see [section 2](#)).
- 1.2 If people with the condition and their healthcare professional consider abaloparatide, romosozumab and teriparatide to be suitable treatments, after discussing the advantages and disadvantages of all the options, the least expensive suitable treatment should be used. Administration costs, dosages, price per dose and commercial arrangements should all be taken into account.
- 1.3 This recommendation is not intended to affect treatment with abaloparatide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

Usual treatments for osteoporosis after menopause include romosozumab or teriparatide and bisphosphonates such as alendronic acid. For this evaluation, the

company asked for abaloparatide to be considered only for people who have a very high risk of fracture. This does not include everyone who abaloparatide is licensed for. It would be used as an alternative treatment to romosozumab or teriparatide.

Clinical trial evidence shows that abaloparatide followed by alendronic acid is more effective at reducing the risk of some types of fracture than placebo followed by alendronic acid. Indirect comparisons suggest that abaloparatide is likely to work at least as well as romosozumab and teriparatide.

The most likely cost-effectiveness estimates for abaloparatide are within the range that NICE considers an acceptable use of NHS resources. So, abaloparatide is recommended.

2 Information about abaloparatide

Marketing authorisation indication

2.1 Abaloparatide (Eladynos, Theramex) is indicated for the 'treatment of osteoporosis in postmenopausal women at increased risk of fracture'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the [summary of product characteristics for abaloparatide](#).

Price

2.3 The list price of abaloparatide is £294.54 per pre-filled pen (excluding VAT, company submission). Each pre-filled pen contains 3 mg abaloparatide in 1.5 ml of solution (30 doses).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes abaloparatide available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The [evaluation committee](#) considered evidence submitted by Theramex, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The condition

Clinical need

3.1 Osteoporosis is a progressive skeletal disorder. It is characterised by low bone density leading to an increased risk of fracture. Fractures can be painful and have a substantial effect on a person's independence. They are also associated with increased mortality. The patient experts said that because of this, people with osteoporosis live in fear of having another fracture. This can lead to them becoming anxious and withdrawn. They said they have difficulty doing day-to-day tasks and can no longer do some things they previously enjoyed, such as going for walks. It can also hinder their ability to care for others, such as their partners. The committee concluded that osteoporosis can have a substantial effect on quality of life.

Treatment pathway and comparators

The population

3.2 The population in the NICE scope and the marketing authorisation is women after menopause with osteoporosis at increased risk of fracture. The population addressed in the company submission is narrower than this regarding fracture risk, because it only includes people at very high risk of fracture. [The National Osteoporosis Guidelines Group \(NOGG\) clinical guideline for the prevention and treatment of osteoporosis](#) defines 'very high risk' as a fracture probability (based on the Fracture Risk Assessment Tool [FRAX]) that exceeds the threshold for intervention by 60%. The company said that abaloparatide would be used at the same place in the treatment pathway as romosozumab or teriparatide. The

company noted that although the marketing authorisation for abaloparatide is for 'treatment of osteoporosis in postmenopausal women', a person can have osteoporosis after menopause and not identify as a woman. The recommendations in this guidance include women, trans men and non-binary people registered female at birth who have osteoporosis after menopause.

Clinical management

- 3.3 The goal of treatment for osteoporosis is to improve bone strength and reduce the risk of fracture. Treatments can be broadly divided into 2 types: anabolic (bone-forming) treatments and antiresorptive treatments (these slow the rate of bone breakdown). People with a very high fracture risk may be offered romosozumab or teriparatide (anabolic treatments). Teriparatide, romosozumab and abaloparatide can only be taken for a limited time (24 months, 12 months and 18 months, respectively). After taking them, people have an antiresorptive treatment (such as an oral bisphosphonate) to maintain the bone mineral density gained during anabolic treatment. The clinical expert said that romosozumab and teriparatide are not suitable for everyone. For example, romosozumab is not used for people with a history of myocardial infarction or stroke. The patient experts said that the existing treatments can have side effects (such as hypercalcaemia and osteonecrosis) which can stop people from taking them. They noted that adherence to treatment is a big problem with osteoporosis. So, the patient and clinical experts agreed that, despite current treatment options, there was still an unmet need for people with a very high risk of fracture when current treatments are not suitable. The company added that teriparatide needs to be stored in a refrigerator which can also be a barrier to adherence, for example when people are travelling. It noted that refrigeration is not needed for abaloparatide after the first use of each injector pen. The committee considered that abaloparatide is taken daily which some people may prefer over taking a monthly treatment (such as romosozumab). The committee concluded

that clinicians, and women, trans men and non-binary people with osteoporosis after menopause would welcome an additional treatment option for osteoporosis with very high risk of fracture.

Comparators

3.4 The company positioned abaloparatide at the same place in the treatment pathway as romosozumab or teriparatide (see [section 3.2](#)). The clinical expert confirmed that abaloparatide would be used as an alternative to these treatments in clinical practice. The committee concluded that romosozumab and teriparatide are appropriate comparators for the population addressed in the company submission.

Clinical evidence

Data sources

3.5 The main source of clinical-effectiveness evidence for abaloparatide was the ACTIVE trial (n=2,463) and its long-term extension study ACTIVEExtend (n=1,139). ACTIVE was a randomised controlled trial which investigated the efficacy and safety of abaloparatide in women after menopause with osteoporosis. The study included healthy women aged 49 to 86 years with osteoporosis after menopause who met 1 of the following criteria:

- T-score between -2.5 and -4.9 at the lumbar spine or femoral neck and radiological evidence of 2 or more mild, or 1 or more moderate, lumbar or thoracic vertebral fractures or history of low-trauma non-vertebral fracture within the past 5 years
- aged over 65 years with the same fracture criteria as the group above, and a T-score between -2.0 and -4.9
- aged over 65 years who did not meet the fracture criteria whose T-score was between -3.0 and -4.9.

People were randomised to 1 of 3 treatment groups for 18 months:

placebo, abaloparatide or teriparatide. Teriparatide was used as an open-label treatment because of its trademarked injection pen, but the other treatments were double-blinded. ACTIVEExtend was a 24-month extension study of ACTIVE that assessed the efficacy and safety of 24 months of alendronic acid after 18 months of abaloparatide or placebo. The EAG noted that ACTIVE included some people who would not be classed as being at very high risk of fracture according to the NOGG clinical guideline (see section 3.2) for the prevention and treatment of osteoporosis. It also included people who did not have a prior fracture, who would not be eligible for teriparatide or romosozumab under current NICE guidance. So, there was uncertainty about whether the treatment effect seen in ACTIVE could be generalised to the population who would be eligible for abaloparatide in the NHS. The clinical expert explained that the treatment benefit of abaloparatide appears to be the same or greater in people at very high risk of fracture (compared with the broader trial population). They said this was biologically plausible, because the bone-forming mechanism of the medicines could work better when there is a greater loss of bone density and structure. The committee noted that it could consider a subgroup analysis of ACTIVE which only included people who would be eligible for abaloparatide in the NHS. But it also noted that the reduced population size would increase the uncertainty of the results. The committee concluded that there were differences between the trial population and the positioning of abaloparatide by the company for use in the NHS. But it agreed that the results from the ACTIVE trial were broadly generalisable to women, trans men and non-binary people at very high risk of fracture after menopause and were suitable for decision making.

Clinical effectiveness and safety

- 3.6 The ACTIVE trial showed that abaloparatide reduced the risk of new vertebral fractures by 88% compared with placebo at 18 months (95%

confidence interval [CI] -0.96 to -0.59, statistically significant). For non-vertebral fractures, the results were not statistically significant for abaloparatide compared with placebo or teriparatide. For major osteoporotic fracture, people having abaloparatide had 69% lower risk of fracture compared with the placebo group at 19 months (hazard ratio [HR] 0.31, CI 0.13 to 0.72, statistically significant). The comparison between abaloparatide and teriparatide was not statistically significant. The results for clinical fracture were non-significant for abaloparatide compared with both placebo and teriparatide. The EAG said the results for ACTIVEExtend were consistent with the findings of the ACTIVE trial. People who had abaloparatide then alendronic acid had an 84% lower risk of 1 or more new vertebral fractures compared with people who had placebo then alendronic acid (relative risk reduction -0.84, CI -0.94 to -0.53, statistically significant). The clinical expert said that the side effect profile for abaloparatide was similar to romosozumab and teriparatide. They noted that the risk of hypercalcaemia was lower with abaloparatide than teriparatide. They also said that no episodes of osteonecrosis were observed within the ACTIVE trials (although this could be because of the relatively small number of people in the study). The patient experts said that osteonecrosis is a significant concern for people with osteoporosis because it is a serious potential side effect of some existing treatments. They said some people have been denied dental treatment because of their dentist's concern about the risk of osteonecrosis. So, the apparent lower risk of osteonecrosis with abaloparatide was a meaningful benefit for people. The committee concluded that abaloparatide is an effective treatment with a similar safety profile to existing treatments overall.

Real-world evidence

- 3.7 To supplement the ACTIVE data, the company also included results from a real-world evidence (RWE) study in its submission. It was a 19-month retrospective observational study from the US which compared abaloparatide with teriparatide (n=23,232). The study results showed that

abaloparatide was statistically non-inferior to teriparatide for time to first non-vertebral fracture (HR 0.89, CI 0.77 to 1.03). It also showed that abaloparatide reduced the risk of hip fracture by 22% compared with teriparatide (HR 0.78, CI 0.62 to 1.00). The committee concluded that the RWE provided useful additional information on the efficacy of abaloparatide compared with teriparatide to support its decision making.

Network meta-analysis

3.8 The ACTIVE study included a direct randomised comparison of abaloparatide with teriparatide. But it was not possible to compare the treatments for all outcomes because the sample size was too small to provide sufficient power. Because of the lack of head-to-head evidence comparing abaloparatide with teriparatide and other relevant comparators, a network meta-analysis (NMA) was done. The NMA included 25 studies and considered 6 outcomes for 10 treatments. The company's findings from the NMA suggested that abaloparatide had comparable efficacy to other non-bisphosphonates (teriparatide, romosozumab and denosumab) and bisphosphonates (alendronic acid and risedronate) for reducing fractures. The committee noted that abaloparatide had the greatest reduction in new vertebral fractures of all treatments compared with placebo. The EAG said that some of the comparisons were based on very few events, which made the results uncertain. For example, for hip fracture the treatment effect of abaloparatide compared with placebo was based on 1 fracture in the placebo arm and 0 fractures in the abaloparatide arm. It also noted that for non-vertebral fractures, the NMA results were inconsistent with the findings from the RWE study. The exact results of the NMA are commercial in confidence and cannot be reported here. The committee concluded that the NMA was useful for decision making but there was uncertainty in the treatment benefit of abaloparatide compared with the other treatments for some fracture types.

Economic model

Company's model structure

3.9 The company used a state-transition individual-level microsimulation model to estimate the cost effectiveness of abaloparatide compared with teriparatide and romosozumab. The model included 5 health states: at risk of fractures, hip fracture, vertebral fracture, non-hip non-vertebral fracture and death. In the company's model, the risk of having a fracture was based on a combination of 4 components: the general population risk of fracture, the increased fracture risk associated with the person's baseline characteristics (based on the FRAX algorithm), the increased fracture risk of a subsequent fracture because of having an incident fracture, and the reduction in risk from osteoporosis treatment. It was assumed that people would have 1 course of anabolic treatment (teriparatide, romosozumab or abaloparatide) over their lifetime. The committee concluded that the model was appropriate for decision making.

Treatment effects used in the model

3.10 Of the 6 outcomes included in the NMA, 3 were used to inform the economic model (new vertebral fractures, non-vertebral fractures and hip fractures). The treatment effect was applied for the duration of each anabolic treatment (abaloparatide, teriparatide and romosozumab) and this duration varied between them (18 months for abaloparatide, 24 months for teriparatide and 12 months for romosozumab). This was because of differences in their treatment licences. The clinical expert said that although people only take the anabolic treatments for a limited amount of time, they change the long-term trajectory of their fracture risk. So, the benefit obtained while on the anabolic treatment continues after the transition to antiresorptive treatments. The EAG said that because of the uncertainties in the NMA (see [section 3.8](#)) it preferred to assume that abaloparatide has the same efficacy as teriparatide for hip and non-vertebral fracture outcomes. They noted that because of the high costs and quality of life impact associated with hip fractures, this was the

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outcome that had the largest impact on the cost-effectiveness results. The committee said that while taking the ACTIVE data, NMA and RWE into consideration, it was unclear whether abaloparatide was more effective than romosozumab and teriparatide overall. This was because of low numbers of some fracture events, some non-significant results, and the inconsistent direction of treatment effects between the RWE and the NMA. So, there was uncertainty in the treatment effect of abaloparatide compared with romosozumab and teriparatide across the outcomes used in the model. The committee concluded that it was conservative to assume that all 3 treatments (abaloparatide, romosozumab and teriparatide) have the same treatment effect. But it would consider the hazard ratios from the NMA as well as the assumption of equal efficacy for all 3 treatments.

Exploring uncertainty in treatment effects

3.11 The company did a probabilistic sensitivity analysis to explore uncertainty in the model. The hazard ratios used for the treatment effect were sampled for each treatment independently from a gamma distribution. The EAG said that the company's approach may have substantially underestimated the uncertainty in the treatment effects and cost-effectiveness estimates. To address this, the EAG preferred to use the convergence diagnostics and output analysis (CODA) samples from the NMA. The company agreed that this was a better approach and accepted the EAG's method. The committee concluded that it preferred the EAG's approach, which used the CODA samples in the probabilistic sensitivity analysis.

Other assumptions

Treatment persistence rates

3.12 The company base case assumed that 80% of people were still taking romosozumab 6 months and 12 months after they started treatment. It said this approach was consistent with [NICE's technology appraisal](#)

[guidance on romosozumab for treating severe osteoporosis](#). The EAG said that a linear decline in treatment persistence had been assumed for abaloparatide and teriparatide, so the same approach should be applied for romosozumab. The EAG base case assumed a linear decline from 0 to 12 months, with 90% of people still taking romosozumab at 6 months and 80% at 12 months. The committee noted that, because of the differences in mechanism of action between the treatments, it was plausible for them to have different persistence rates. The concluded that both assumptions (linear and non-linear decline) would be considered.

Costs and resource use

3.13 The company and the EAG had different preferences for some of the unit costs. They also had small differences in resource use. For example, the EAG preferred to assume that people had a bone density (DEXA) scan at the start and the end of anabolic treatment (12, 18 or 24 months, depending on the treatment). But the company assumed that people had a DEXA scan every 2 years. The clinical expert advised that having a DEXA scan at the start and end of anabolic treatment was reasonable and aligned with their clinical practice. This enabled them to see if the treatment benefits gained by the end of the initial anabolic treatment were maintained after the transition to antiresorptive treatment. But they also noted that there were variations in practice across the NHS. The committee concluded that both the EAG and company assumptions would be considered.

Utility values

3.14 The company base case did not include a specific reduction in quality of life for people who went into long-term care because of a hip fracture. The utility value used for people with a hip fracture did account for a proportion of people going into long-term care, but this was applied at a cohort level rather than individual level. The patient experts confirmed that having to go into long-term care and losing their independence would have a large

negative impact on their quality of life. They saw this as a last resort and would avoid it unless absolutely necessary (for example by using home care instead). The EAG adapted the model so that risk of long-term admission was applied at an individual level, rather than cohort level. This enabled it to conduct a scenario analysis in which a utility multiplier of 0.625 was applied to people going into long-term care after a hip fracture. But it noted that the utility value being used for hip fracture already assumed that a proportion of people would go into long-term care. So, adding an additional decrement would result in some double counting. The company said it hadn't included a specific decrement in its base case because of this risk of double counting but agreed that care home admission has a significant impact on quality of life. The committee concluded that it would consider both options (that is, the cohort-level approach without the specific utility decrement, and the individual-level approach with the utility decrement) in its decision making.

Cost effectiveness

Incremental net health benefits

3.15 Cost effectiveness was assessed by calculating net health benefit. This was because the incremental cost-effectiveness ratios (ICERs) were extremely unstable. Different scenarios had very small differences in incremental quality-adjusted life years (QALYs), and this meant that small differences in the costs resulted in large fluctuations in the ICERs. Also in some scenarios, abaloparatide had lower total costs and lower total QALYs than the comparators. Net health benefit can be a more useful and informative figure than ICERs in this case. The net health benefit (at a threshold value of £20,000 per QALY gained), total costs and total QALYs of abaloparatide were compared with those of romosozumab and teriparatide using pairwise comparisons.

Preferred assumptions

3.16 The incremental benefit of abaloparatide over romosozumab and teriparatide was considered by comparing the size of the net health benefit for each comparison. The committee noted that there was uncertainty around the treatment effect of abaloparatide compared with romosozumab and teriparatide. It explored this uncertainty through a range of scenarios. These included a scenario using the hazard ratios from the NMA, a scenario that assumed equal efficacy for some comparisons, and a scenario assuming equal efficacy for all comparisons. The committee felt it was unlikely that this uncertainty could be resolved using any currently available data, or any data planned to be collected in the near future. Different preferred assumptions between the company and the EAG about treatment persistence, long-term care costs and resource use were also considered. The committee noted the probabilistic sensitivity analyses done by the company and the EAG, and preferred the use of the NMA CODA samples. So, several different sets of assumptions were considered by the committee. But it observed that changes in the preferred assumptions typically had very little impact on the costs, QALYs or net health benefits. The price for 1 of the comparators differed between NHS regions (because it is negotiated by the Medicines Procurement and Supply Chain, formerly the Commercial Medicines Unit). So, the committee also considered analyses based on both the lowest and the highest available prices in its decision making (see [section 4.4.5 of NICE's manual on health technology evaluations](#)). For most scenarios considered by the committee, there was a positive incremental net health benefit for abaloparatide compared with teriparatide and romosozumab. In some scenarios, abaloparatide generated more QALYs at a lower cost than its comparators. Because of confidential commercial arrangements for abaloparatide and the comparator treatments in the pathway, the exact net health benefits cannot be reported here. The committee concluded that the most likely cost-effectiveness estimates for abaloparatide compared with romosozumab and teriparatide were within the range that NICE considers an acceptable use of NHS resources.

Other factors

Equality

- 3.17 The company noted that although the marketing authorisation for abaloparatide is for ‘treatment of osteoporosis in postmenopausal women’, a person can have osteoporosis after menopause and not identify as a woman. Gender reassignment is a protected characteristic under the Equality Act 2010. The recommendations in this guidance include women, trans men and non-binary people registered female at birth (see [section 1.1](#)).

4 Implementation

- 4.1 [Section 7 of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication or commercial availability of the product.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance or commercial availability of the product.
- 4.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has osteoporosis after menopause and the healthcare professional responsible for their care thinks that abaloparatide is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The [minutes of each evaluation committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Radha Todd

Chair, technology appraisal committee A

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Alex Sampson

Technical lead

Nigel Gumbleton

Technical adviser

Vonda Murray

Project manager

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