NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA464; Bisphosphonates for treating osteoporosis

Original publication date:	August 2017
Review date	August 2020
Existing recommendations:	Optimised To see the complete existing recommendations and the original remit for TA464, see Appendix A.

1. Proposal

To update and re-issue the guidance. To consult on this proposal.

2. Rationale

TA464 currently recommends oral bisphosphonates for people with at least a 1% 10-year risk of fracture, and intravenous bisphosphonates for people with at least a 10% 10-year risk of fracture (see section 4 for full recommendations).

The Medicines and Healthcare products Regulatory Agency (MHRA) has raised concerns that the current recommendations may lead to wide use of bisphosphonates (oral and intravenous) in a population at low risk of fracture, outside of the supporting evidence. It further commented that it is unclear if fracture risk in these patients will be reduced by bisphosphonate treatment and therefore, in this low-risk population, the risk–benefit balance may not be favourable. In particular, long-term treatment may lead to rare but serious adverse reactions.

The MHRA has highlighted that:

- the minimum fracture risk for the supporting trials was around 10%,
- current published intervention thresholds recommend treatment from much higher levels of fracture risk than 1%, such as the National Osteoporosis Guideline Group (NOGG) guidelines, in which treatment is recommended from a risk of between approximately 7 and 25%, depending on age.

The population considered in TA464 was “Adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE clinical guideline 146”. This population was selected to align the technology appraisal with the clinical

guideline. Not all of those who are assessed for risk will be found to have an increased risk of fracture and require treatment. Therefore the population for whom it is clinically appropriate to treat is a subgroup of the population considered within the appraisal. This broad approach was taken because there is currently no clear consensus on the risk at which a person requires treatment. Therefore a population for whom it is clinically appropriate to treat could not be defined. In addition the marketing authorisations for the technologies do not specify a fracture risk for starting treatment.

The recommendations made in TA464 represent a health economic threshold (i.e. the point at which it is cost effective to use the technology), rather than an intervention threshold (i.e. the point at which it is clinically appropriate to consider using the technology). This has been clarified on the landing page of the guidance, where it states:

'The purpose of this technology appraisal was to establish at what level of absolute fracture risk bisphosphonates are cost effective. Please note that because of the reduction in prices for oral bisphosphonates over the last few years, the absolute risk level at which these drugs are cost effective is now very low. ***The absolute risk level at which oral bisphosphonates are recommended as treatment options in this guidance are therefore not clinical intervention thresholds.*** *This technology appraisal guidance should be applied clinically in conjunction with:*

- *NICE guideline on assessing the risk of fragility fractures (CG146) that defines who is eligible for osteoporotic fracture risk assessment.*
- *NICE quality standard on osteoporosis (QS149) that defines the clinical intervention thresholds for the 10-year fracture probability of a major osteoporotic fracture, in those patients who have undergone fracture risk assessment. These thresholds are based on the NICE-accredited National Osteoporosis Guideline Group guideline.*
- *The individual person's circumstances, goals and informed preferences.'*

However, it is clear from the MHRA that the recommendations continue to be interpreted as a clinical intervention threshold. To address this, we propose removing the risk score from the guidance and emphasise the need to apply clinical judgement in considering when treatment should be started.

3. Process for the update

An update to the recommendations in the guidance should be planned into the appraisal work programme. This update can be done without going through a full appraisal process and involve the following steps:

- Develop new draft wording for the recommendations (reducing from 5 discreet sections to 3) and landing page on the NICE website (see section 3 below)

- Expose the draft recommendations to stakeholders, and clinical, patient, and NHS experts (as part of the consultation on this review proposal)
- Seek committee ratification of the new wording of the recommendations (post engagement with stakeholders, and clinical, patient, and NHS experts).
- Issue an ACD or FAD (should the committee diverge substantively from the draft wording that went out for consultation or the suggestions made by stakeholders during the consultation, we would consult on the preliminary new recommendations; otherwise we will issue the new recommendations as an update to TA464, in a FAD for appeal).

4. Proposed updated recommendations

It is suggested that the recommendations are re-worded to:

1. *Oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium) and intravenous bisphosphonates (ibandronic acid and zoledronic acid) are recommended, with their marketing authorisations, as options for treating osteoporosis in adults*

    a. *who are eligible for risk assessment as defined in NICE's guideline on osteoporosis (recommendations 1.1 and 1.2) and the NICE Quality Standard on osteoporosis and*

    b. *who have been assessed as being at higher risk of osteoporotic fragility fracture using the methods recommended in NICE's guideline on osteoporosis (recommendations 1.3 to 1.12) and the NICE Quality Standard on osteoporosis and*

    c. *when bisphosphonate treatment is appropriate, taking into account their risk of fracture, their risk of adverse effects from bisphosphonates, and their clinical circumstances and preferences.*

2. *The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient, or their carers, about the advantages and disadvantages of the treatments available. If generic products are available, start treatment with the least expensive formulation, taking into account administration costs, the dose needed and the cost per dose.*

3. *These recommendations are not intended to affect treatment with alendronic acid, ibandronic acid, risedronate sodium and zoledronic acid that was started in the NHS before this guidance was published. Adults having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.*

The wording on the landing page should also be amended to the following:

'The purpose of this technology appraisal was to establish at what level of absolute fracture risk bisphosphonates are cost effective. Please note that because of the

reduction in prices for oral bisphosphonates over the last few years, the absolute risk level at which these drugs are cost effective is now very low. The absolute risk level at which oral bisphosphonates are cost effective as treatment options do not represent clinical intervention thresholds. This technology appraisal guidance should be applied clinically in conjunction with:

- *NICE guideline on assessing the risk of fragility fractures (CG146) that defines who is eligible for osteoporotic fracture risk assessment.*
- *NICE quality standard on osteoporosis (QS149) that defines the clinical intervention thresholds for the 10-year fracture probability of a major osteoporotic fracture, in those patients who have undergone fracture risk assessment. These thresholds are based on the NICE-accredited National Osteoporosis Guideline Group guideline.*
- *The individual person's circumstances, goals and informed preferences.'*

5. Risks/consequences

It could be argued that removing the minimum risk score could further expand use of bisphosphonates for osteoporosis to those with a risk score below 1% for oral bisphosphonates or below 10% for intravenous bisphosphonates, and therefore to populations for which the use is not considered cost effective. However, the advice we have received from the MHRA, clinical and patient experts is that for people with such a low risk of fracture, treatment wouldn't generally be considered clinically appropriate. Moreover, this change should encourage clinical judgement to be applied to the guidance and therefore reduce overuse of bisphosphonates.

GE paper sign off: **Helen Knight 10.01.19**

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Appendix A – Information from existing guidance

6. Original remit

To appraise the clinical and cost effectiveness of alendronate, etidronate, risedronate, zoledronate and ibandronate, within their licensed indications, for the prevention of osteoporotic fragility fractures.

7. Current guidance

The purpose of this technology appraisal was to establish at what level of absolute fracture risk bisphosphonates are cost-effective. Please note that because of the reduction in prices for oral bisphosphonates over the last few years, the absolute risk level at which these drugs are cost-effective is now very low. The absolute risk level at which oral bisphosphonates are recommended as treatment options in this guidance are therefore not clinical intervention thresholds. This technology appraisal guidance should be applied clinically in conjunction with:

- NICE guideline on assessing the risk of fragility fractures (CG146), which defines who is eligible for osteoporotic fracture risk assessment.
- NICE quality standard on osteoporosis (QS149), which defines the clinical intervention thresholds for the 10-year fracture probability of a major osteoporotic fracture, in those patients who have undergone fracture risk assessment. These thresholds are based on the NICE-accredited National Osteoporosis Guideline Group guideline.
- The individual person's circumstances, goals and informed preferences.

Further information is in the implementation section.

1.1 Oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium) are recommended as options for treating osteoporosis in adults only if:

- the person is eligible for risk assessment as defined in NICE's guideline on osteoporosis (recommendations 1.1 and 1.2) and
- the 10-year probability of osteoporotic fragility fracture is at least 1%.

1.2 Intravenous bisphosphonates (ibandronic acid and zoledronic acid) are recommended as options for treating osteoporosis in adults only if:

- the person is eligible for risk assessment as defined in NICE's guideline on osteoporosis (recommendations 1.1 and 1.2) and
- the 10-year probability of osteoporotic fragility fracture is at least 10% or
- the 10-year probability of osteoporotic fragility fracture is at least 1% and the person has difficulty taking oral bisphosphonates (alendronic acid, ibandronic acid or risedronate sodium) or these drugs are contraindicated or not tolerated.

1.3 Estimate the 10-year probability of osteoporotic fragility fracture using the FRAX or QFracture risk tools, in line with NICE's guideline on osteoporosis.

1.4 The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient, or their carers, about the advantages and disadvantages of the treatments available. If generic products are available, start treatment with the least expensive formulation, taking into account administration costs, the dose needed and the cost per dose.

1.5 These recommendations are not intended to affect treatment with alendronic acid, ibandronic acid, risedronate sodium and zoledronic acid that was started in the NHS before this guidance was published. Adults having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Alendronic acid, ibandronic acid, risedronate sodium and zoledronic acid are bisphosphonates, licensed for treating osteoporosis. Currently clinicians offer bisphosphonates to people with osteoporosis who are eligible for risk assessment and who have a high fracture risk.

To simplify the criteria for treatment and bring the guidance into line with NICE's guideline on osteoporosis, the evidence on bisphosphonates has been reviewed. A new network meta-analysis confirms that bisphosphonates are more effective at reducing the risk of fracture than placebo.

Risk assessment tools are used in clinical practice (FRAX and QFracture), in line with NICE's guideline on osteoporosis. These tools measure risk differently and can give different levels of risk in the same person.

Oral bisphosphonates are recommended because new analyses show they are cost effective for people with at least a 1% risk of osteoporotic fragility fracture, irrespective of the assessment tool used. Similarly, intravenous bisphosphonates are recommended because they are cost effective for people with at least a 10% risk of osteoporotic fragility fracture, irrespective of the risk assessment tool used.

For some people with a 1% risk of osteoporotic fragility fracture, oral bisphosphonates may be contraindicated or not tolerated, or taking them might be difficult or impossible. For these people intravenous bisphosphonates are recommended.

8. Research recommendations from original guidance

N/A.

9. Cost information from original guidance

N/A