NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Review Proposal Project (RPP) decision paper

Review of TA464; Bisphosphonates for treating osteoporosis

Final recommendation post consultation
To update and re-issue the guidance. The recommendations in TA464 should be reworded 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.'*

1. Background

This guidance was issued in August 2017.

At the Guidance Executive meeting of 12 February 2019 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

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

3. Rationale for selecting this proposal

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.

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: Merck Sharp & Dohme Limited **Response to proposal:** No comment MSD does not have any comments on the proposed updates for bisphosphonates for treating osteoporosis.	**Comment from Technology Appraisals** Thank you for your response.

Respondent: The Royal College of Pathologists **Response to proposal:** Agree The proposal to update and re-issue the existing guidance on Bisphosphonates for treating osteoporosis is a very welcome and appropriate clarification from NICE in this area.	**Comment from Technology Appraisals** Thank you for your comment.

Respondent: Royal Osteoporosis Society **Response to proposal:** Agree We are delighted that NICE have recognised the need for change and welcome the proposal to remove the risk score from the guidance and emphasise the need to apply clinical judgement in considering when treatment should be started. Please see below our comments/concerns based on feedback from our clinical experts: • Intervention thresholds: We have concerns that the reworded recommendations have resulted in a lack of guidance around intervention thresholds. Guidance should not simply point to other documents/websites (i.e. NICE Quality Standards), as this makes it a complex, multi-step procedure for busy clinicians and information could easily be missed. We suggest that it should explicitly state in the main recommendations section (paragraph 4.1.b; Appendix A) that the intervention thresholds should be those produced by the NICE-accredited NOGG guidelines. • FRAX underestimation of fracture risk: We suggest that the guidance should be explicit about those circumstances in which FRAX underestimates fracture risk an highlight the need for clinical judgement in making the decision whether to offer treatment e.g. in the presence of vertebral fragility fractures and in patients requiring high-dose glucocorticoids.	**Comment from Technology Appraisals** Thank you for your comment. The purpose of this technology appraisal was to establish at what level of absolute fracture risk bisphosphonates are cost effective. It was not within the remit of the appraisal to make recommendations on clinical intervention thresholds. Therefore, explicit reference to clinical intervention thresholds and guidance on interpreting FRAX cannot be made in the recommendations section of TA464. The proposed updated wording for the landing page for TA464 makes reference to the National Osteoporosis Guideline Group guideline: '*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'.* Further, the NICE quality standard on osteoporosis, which defines the clinical intervention thresholds for the 10-year fracture probability of a major osteoporotic fracture based on the NICE-accredited National Osteoporosis, is included in the

	recommendations section of the updated wording for TA464.

Respondent: British Society of Rheumatology	**Comment from Technology Appraisals**
Response to proposal: Agree The existing guideline quotes 10 year fracture risks at which oral and parenteral bone treatments are considered cost effective (1% and 10% respectively) from a health economic perspective. We agree that these figures should be removed entirely because they have been widely misinterpreted by non-specialists as investigation and/or treatment thresholds, and caused significant difficulty at commissioning level. We believe that treatment decisions should be based upon clinical assessment of fracture risk, taking into account all relevant risk factors for an individual patient. This should take into account clinical judgement, patient preferences and relevant local / national guidelines (e.g. the NICE accredited FRAX / NOGG guidance).	Thank you for your comment.

Paper signed off by: Nicole Elliott, 09 April 2019

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