

2022 exceptional surveillance of early and locally advanced breast cancer: diagnosis and management (NICE guideline NG101)

Surveillance proposal

We will not update [section 1.9 bisphosphonate therapy](#), the use of adjuvant bisphosphonates in people with early or locally advanced breast cancer in the guideline on [early and locally advanced breast cancer](#).

Reason for the exceptional review

The purpose of this exceptional review was to examine any impact on NICE's guideline on early and locally advanced breast cancer of published evidence on the indications for using adjuvant bisphosphonates in people with early or locally advanced breast cancer.

Methods

The exceptional surveillance process consisted of:

- Considering the evidence used to develop the guideline in 2018.
- Considering the new evidence that triggered the exceptional review.
- A focused literature search to identify relevant evidence on adjuvant bisphosphonate therapy in people with early or locally advanced breast cancer.
- Examining related NICE guidance.
- Examining the NICE event tracker for relevant ongoing and published events (none identified as relevant on 29th April 2022).
- Feedback from topic experts.
- Assessing the new evidence and topic expert feedback against current recommendations to determine whether or not to update the section on adjuvant bisphosphonate therapy in NICE guideline NG101.
- Consulting on the proposal with stakeholders.
- Considering comments received during consultation and making any necessary changes to the proposal.

For further details about the process and the possible update decisions that are available, see [ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual](#).

Evidence considered in this exceptional surveillance review

Information considered when developing the guideline

The evidence review on the use of adjuvant bisphosphonates in people with early and locally advanced breast cancer was concerned with the effect of bisphosphonates on breast cancer specific outcomes (see [evidence review G: adjuvant bisphosphonate](#)). The critical outcomes were overall survival (OS), disease-free survival (DFS), and treatment-related morbidity (particularly osteonecrosis of the jaw, because of its severity).

Bone health, treatment-related mortality and health-related quality of life (HRQoL) were identified as important outcomes; however bone health was only included to check whether the new evidence was consistent with existing recommendations for the use of bisphosphonate treatment for bone loss (see recommendation 1.9.6 which references [Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK expert group](#)).

A literature search was undertaken for systematic reviews or meta-analysis of randomised control trials (RCTs) and RCTs published up to September 2017 that could answer the review question “what are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?” Included bisphosphonates were: alendronic acid/alendronate, sodium clodronate, pamidronate disodium, ibandronic acid/ibandronate, zoledronic acid/zoledronate, and risedronate sodium/risedronate.

Twenty articles (number of participants, n=33,051) were included in the review of evidence reported in RCTs and a systematic review). The quality of the evidence was assessed using GRADE.

Bone health evidence was of mixed quality (high to very low) and was found to be consistent with existing recommendations to use bisphosphonate treatment for bone loss. There was limited, very low-quality evidence on HRQoL which reported no effect of bisphosphonate treatment on HRQoL. No evidence was found for treatment-related mortality.

For the critical outcomes of OS and DFS the evidence was assessed as moderate to high quality. However, it was reported in the evidence review that “it was not possible to judge the quality of evidence for a number of the subgroups as the number of people and/or number of events of interest were not reported in some papers, and so it was not possible to determine the imprecision around the estimate, and therefore the overall quality”.

The only clinical meaningful effects found for OS and DFS were for the bisphosphonates zoledronic acid and sodium clodronate:

- zoledronic acid significantly increased DFS at 5.6 years follow-up compared with no treatment in postmenopausal women with invasive breast cancer (n=3,622; high quality evidence)
- zoledronic acid significantly increased DFS at 5.2 years follow-up compared with no treatment in people with node-positive invasive breast cancer (n=550; moderate quality evidence)
- sodium clodronate resulted in a significant increase in OS at 5.6 years follow-up compared with placebo for women with invasive breast cancer (n=4,402; high quality evidence)
- sodium clodronate resulted in a significant increase DFS at 5.6 years follow-up compared with placebo for postmenopausal women with invasive breast cancer (n=1,833; moderate quality evidence)

An economic analysis was developed to estimate the cost-effectiveness of various bisphosphonates in the treatment of early and locally advanced breast cancer (all cases), and in node-positive and postmenopausal populations. The analysis was based on OS and DFS estimates for each of the treatments

included in the analysis. The following were found to be cost-effective at the NICE threshold of £20,000 per QALY:

- for the overall population: sodium clodronate (and risedronate) compared against no treatment. (Note: risedronate was also found to be cost-effective when compared against sodium clodronate. However, risedronate was not found to be an effective treatment based on clinical evidence, which therefore limits the reliability of the base case estimates in the economic analysis; and makes it difficult to draw any firm conclusion around cost-effectiveness as the clinical evidence upon which it is based is too uncertain).
- for the node-positive population (regardless of menopausal status): zoledronic acid and sodium clodronate compared against no treatment. For this population, zoledronic acid was less costly and more effective than sodium clodronate.
- for the postmenopausal population: zoledronic acid, sodium clodronate (and ibandronate) compared against no treatment. Comparing all strategies against each other, it was found that sodium clodronate would be the preferred strategy in cost-effectiveness terms.

The guideline development group (GDG) noted that while the health economic results showed that bisphosphonates may be cost-effective, especially in higher risk populations, there was a high degree of uncertainty around the clinical inputs upon which the analysis was based; but that “the analysis gives an indication that the cost-effectiveness results largely mirror the clinical effectiveness inputs. Therefore, if bisphosphonates were shown to improve overall and disease-free survival then it is likely that their use would be cost-effective.”

Based on the effectiveness and cost-effectiveness evidence the GDG made [recommendation 1.9.1](#) to “offer bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy to postmenopausal women with node-positive invasive breast cancer”.

[Recommendation 1.9.2](#) to “consider bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy for postmenopausal women with node-negative invasive breast cancer and a high risk of recurrence” was supported by the high quality evidence that sodium clodronate produced benefits in OS in mixed populations, but the GDG decided that “a strong ‘offer’ recommendation could not be made due to the fact that for a number of other bisphosphonate comparisons a clinical benefit was not shown”.

Treatment-related morbidity evidence was of mixed quality (high to very low), but there was moderate quality evidence that IV zoledronic acid was associated with a clinically meaningful 1% increase in osteonecrosis of the jaw at 5 years follow-up compared with no treatment control for people with invasive breast cancer (n=3,359). There was no evidence available for osteonecrosis rates after treatment with other bisphosphonates, but the evidence review reported that “it is known that the risk is greatest following IV bisphosphonates” (zoledronic acid is only given by intravenous infusion, whereas sodium clodronate is given orally); and highlighted that “jaw osteonecrosis is a very serious adverse event, can be life changing, and there is no effective treatment, with only conservative management available”. The GDG therefore decided that it was important that the risk of jaw osteonecrosis is discussed with people considering bisphosphonate treatments, and therefore made [recommendation 1.9.3](#) to “discuss the benefits and risks of bisphosphonate treatment with women, particularly the risk of osteonecrosis of the jaw, atypical femoral fractures and osteonecrosis of the external auditory canal” and added a cross reference to the warning from the [Medicines and Healthcare products Regulatory Agency/Commission on Human Medicines \(MHRA/CHM\) advice on bisphosphonates](#) which highlights that “risk factors for developing osteonecrosis of the jaw that should be considered are: potency of bisphosphonate (highest for zoledronate), route of administration, cumulative dose, duration and type of malignant disease, concomitant treatment, smoking, comorbid conditions, and history of dental disease”.

Because of a lack of conclusive evidence on OS and DFS for bisphosphonates other than zoledronic acid and sodium clodronate, the committee decide to make [research recommendation 2](#): “Which groups of people with early and locally advanced breast cancer would benefit from the use of adjuvant bisphosphonates?” This was to encourage research to determine the long-term survival benefits for a wider number of bisphosphonates; and to focus on which subgroups of people with breast cancer (such as premenopausal women, premenopausal women on ovarian suppression, those with node-positive or node-negative disease, and those with positive or negative oestrogen or progesterone statuses) may benefit from adjuvant bisphosphonates.

Evidence that triggered the exceptional review

We received an external enquiry highlighting that new evidence reported in the “Phase III Randomized Trial of Bisphosphonates as Adjuvant Therapy in Breast Cancer: S0307” ([Gralow et al. 2020](#)) may have an impact on recommendations 1.9.1 to 1.9.3 on adjuvant bisphosphonate therapy in NICE guideline NG101.

Methods

This is a phase 3 North American open-label trial comparing the efficacy of 3 years of treatment of either intravenous (IV) zoledronic acid (given monthly for 6 months, then every 3 months; standard dosage was 4 mg, with graduated reduction to 3 mg for renal impairment), oral clodronate (1,600 mg daily), or oral ibandronate (50 mg daily) in 6,097 women aged 18 years or older with stage I-III breast cancer. Patients were recruited between January 2006 and February 2010 (with random assignments to ibandronate stopping in August 2009 because of plans to market the drug at the trial dose being abandoned in North America). Participants were then followed-up for 5 years before final analysis (with all patients followed for 10 years from treatment assignment).

To be included, patients must have received, or planned to receive, systemic adjuvant therapy. Patients were excluded if they had renal failure or history of

prior malignancy (except for specified in situ cancers or other cancers from which they were disease free for ≥ 5 years).

The study changed the target for sample size recruitment (after changes in plans to market ibandronate at 50 mg daily) to 2,000 patients receiving zoledronic acid, 2,000 receiving clodronate, and 1,400 receiving ibandronate over 4 years. The authors reported that the “study was powered to find a statistically significant difference among the 3 arms at two-sided $\alpha=0.05$. This assumed that the worst treatment would have a 5-year DFS of 80% and that the best treatment compared to the worst treatment would have a hazard ratio (HR) of 0.80 (justification for selecting this value was not provided).” The authors reported that they had initially planned to have a no treatment control arm, but decided that clodronate (a nonaminobisphosphonate) would serve as the baseline to compare with the newer aminobisphosphonates (nitrogen-containing bisphosphonates) zoledronic acid and ibandronate and hypothesised that these may be more effective at preventing metastases compared with clodronate.

Results

Of the 6,097 recruited patients, 73 were found to be ineligible and 6 withdrew consent, resulting in data from 6,018 patients included in the analysis: $n=2,231$ for zoledronic acid, $n=2,235$ for clodronate and $n=1,552$ for ibandronate.

Only 60.3% completed all 3 years of bisphosphonate therapy. The study authors reported that the difference between treatment compliance was “small”: for zoledronic acid $n=1,410$ (63.2%), for clodronate $n=1,276$ (57.1%) and for ibandronate $n=943$ (60.8%).

The baseline characteristics of patients (demographics, tumour characteristics, breast cancer stage) did not significantly differ between the treatment arms. Menopausal status was not reported, only whether women were aged less than 55 years of age (57.6 % of participants) or 55 years and older (42.4%). The majority of tumours (78.5%) were hormone receptor positive (oestrogen or progesterone receptor positive) and/or human

epidermal growth receptor 2 (HER2) status was negative (80.1%). Breast cancer stage was unknown for 142 of participants (2.3%), 33.2% were stage 1, 43.9% stage 2 and 20.5% stage 3. Chemotherapy and/or endocrine therapy was used or planned in 79.6% and 75.2% of women respectively. DFS (starting at 3 years) was compared across treatment arms and according to whether women had completed therapy (“completers”) or not (“non-completers”). A log-rank test at 3 years found no significant differences in DFS between the treatment arms for completers compared with non-completers; but did find that, when adjusted for treatment, completers were significantly less likely than non-completers to have a DFS event after 3 years. This comparison between completers and non-completers was not reported for the 5-year DFS. The study authors reported that there were no significant differences between treatment arms in 5-year DFS: in the zoledronic acid treatment group DFS was 88.3% (95% confidence interval (CI)=86.9% to 89.6%), for clodronate 87.6% (95% CI=86.1% to 88.9%), and ibandronate 87.4% (95% CI=85.6% to 88.9%). A univariate Cox model comparing treatments, gave the following (non-significant) pairwise hazard ratios (HR): clodronate versus zoledronic acid HR=1.09, 95% CI=0.94 to 1.26; ibandronate versus zoledronic acid HR=1.06, 95% CI=0.90 to 1.24 (comparison of clodronate versus ibandronate not reported).

For secondary outcomes, there were no significant differences between the treatment groups for 5-year OS (for zoledronic acid this was 92.6%, 95% CI=91.4% to 93.6%; for clodronate 92.4%, 95% CI=91.2% to 93.5%, and for ibandronate 92.9%, 95% CI=91.5% to 94.1%). Nor were there any significant differences between the treatment groups for bone as first site of recurrence; and there were no treatment differences related to age, tumour subtypes, or any other baseline characteristics. While the study reported that 5-year DFS was 89.9% for patients with hormone receptor positive subtypes (irrespective of HER2 status), 85.3% for patients HER2 positive and hormone receptor negative and 78.4% for patients with triple-negative subtypes, no statistical analysis was reported on comparisons of efficacy between different patients with different baseline characteristics to determine whether bisphosphonates may be more beneficial in specific groups of people with breast cancer.

For treatment-related morbidity, osteonecrosis of the jaw was significantly higher in patients receiving zoledronic acid (1.26%) compared with clodronate (0.36%) or ibandronate (0.77%) (analysis of this data is described in a separate publication, see evidence summary below and Appendix A). In relation to non-completers, only 10.0% of women receiving zoledronic acid stopped treatment because of toxicity or serious adverse events, whereas this was 17.0% for clodronate and 17.2% for ibandronate (statistical analysis of difference not reported).

Discussion

While this RCT provides evidence which indicates that there is no difference in DFS or OS in people with stage I-III breast cancer treated with adjuvant zoledronic acid, clodronate or ibandronate, and that there are low levels of treatment-related morbidity, there are several limitations to the study. This phase 3 trial was an open-label trial, so both researchers and participants were aware of which treatment was being administered, it assessed the benefits of treatment under ideal conditions (efficacy rather than effectiveness), with neither a placebo nor 'no treatment' arm to compare results with, which meant, as noted by the study authors, that 'this trial does not allow assessment of the degree of benefit bisphosphonates offer, if any, in early-stage breast cancer'; and the assessment of DFS at 3 years between completers and non-completers of the adjuvant bisphosphonate treatment should not be considered as a proxy for a control group. In addition, while the high level of 5-year DFS across all groups is an encouraging result, the sample size and study power analysis assumed that 'the worst treatment would have a 5-year DFS of 80% and that the best treatment compared to the worst treatment would have a hazard ratio (HR) of 0.80'; as DFS values were considerably higher and did not differ between treatments, the study may be underpowered.

Although the study findings suggest that ibandronate might be an alternative treatment option to zoledronic acid or clodronate, analysis by breast cancer subgroups is not provided, thereby not addressing the recommendation for research in NICE guideline NG101; and the study limitations are such that,

based on this study alone, we would not propose an update of recommendations on adjuvant bisphosphonate treatment in NICE guideline NG101 to consider the inclusion of ibandronate as a treatment option for people with early or locally advanced cancer. However, given that the evidence on which recommendations 1.9.1 to 1.9.3 were based on has not been reviewed since 2017, we decided that we should assess whether there is additional RCT evidence that could inform our decision, and so we decided to undertake a search for new evidence.

2022 focused literature search on adjuvant bisphosphonate therapy

Search and selection strategy

We searched for new evidence related to the evidence review question “What are the indications for using adjuvant bisphosphonates in people with early and locally advanced breast cancer?” The search strategy was the same as that used in the development of recommendations 1.9.1 to 1.9.3 on adjuvant bisphosphonate therapy in 2018 for NICE guideline NG101 (see appendix B of [evidence review G: adjuvant bisphosphonate](#)).

We found 735 studies in a focused search for systematic reviews, meta-analyses of RCTs, and RCTs published between 26th September 2017 (the end date for the search period for NICE guideline NG101) and 29th April 2022 (3rd May 2022 for CENTRAL database due to the download function not working on 29th April 2022).

The selection criteria were the same as those in “evidence review G: adjuvant bisphosphonate” (see Table 1 for the population, intervention, comparison and outcome inclusion criteria). Phase 2 trials were excluded.

We considered 15 studies to be relevant to the review question, including the S0307 RCT that triggered this evidence review (Gralow et al. 2020; see evidence that triggered the exceptional review) and another study reporting in more detail on osteonecrosis of the jaw in patients in the S0307 RCT ([Kizub et](#)

[al. 2021](#)). We also included 1 Cochrane review, 6 systematic reviews/meta-analyses/network meta-analyses and 6 studies reporting on individual RCTs.

See [appendix A](#) for summary details of included studies.

Evidence summary

Overall survival and disease-free survival

A Cochrane review ([O'Carrigan et al. 2017](#)), 1 systematic review ([Liu et al. 2021](#)) and 4 RCTs ([De Groot et al. 2019](#), [Coleman et al. 2017](#), [Paterson et al. 2021](#) and [Vliek et al. 2022](#)) reported on OS and/or DFS in people with early or locally advanced breast cancer treated with adjuvant bisphosphonates.

The Cochrane review evidence includes evidence published before the end of the search period for the evidence review on adjuvant bisphosphonates for NICE guideline NG101. Its findings on OS and/or DFS support recommendations 1.9.1 and 1.9.2 to provide zoledronic acid or sodium clodronate to postmenopausal women with early and locally advanced breast cancer, but a sub-group analysis based on evidence of whether postmenopausal patients had node-positive or node-negative invasive breast cancer was not undertaken. The recent systematic review by Liu et al. 2021 report on a meta-analysis of evidence from 17 RCTs which indicate there is an OS benefit for people with breast cancer who have 'no evidence of any relapse or metastasis'.

Findings from 1 RCT (De Groot et al. 2019) indicate that zoledronic acid does not improve DFS in women with HER2-negative, stage II or III breast cancer, and may be associated with worse OS.

There is also evidence from 2 RCTs (Coleman et al. 2017 and Paterson et al. 2021) that indicates that assessing MAF amplification (a biomarker for bone metastasis) in primary tumours could help in treatment decisions as evidence indicates that breast cancer patients with MAF-positive tumours do not benefit from zoledronic acid or sodium clodronate, while those with MAF-negative tumours show significant survival benefits. In addition, zoledronic acid may be associated with a decrease in survival outcomes for premenopausal patients

with MAF-positive tumours. These publications were retrospective analyses on a sub-set of participants in two trials, whose 5-year follow-up data had been included in [evidence review G on adjuvant bisphosphonate](#): the AZURE trial and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-34.

Evidence from 1 RCT (Vliek et al. 2022) indicates that adjuvant ibandronate is not associated with improvements in DFS in postmenopausal women with oestrogen receptor positive stage I to III breast cancer.

Treatment-related morbidity

A Cochrane review (O'Carrigan et al. 2017), 2 systematic reviews ([Yang et al. 2019](#) and [Jackson et al. 2021](#)) and 1 RCT (Kizub et al. 2021) reported on morbidity associated with adjuvant bisphosphonates. Overall, the evidence indicated that osteonecrosis of the jaw does occur with the use of adjuvant bisphosphonates, with systematic review evidence indicating it occurs in around 0.5% of breast cancer patients on adjuvant bisphosphonates, and the evidence overall indicates that osteonecrosis of the jaw is significantly more likely to occur with the use of IV zoledronic acid compared with oral bisphosphonates.

Bone health

Six publications reported on the effect of adjuvant bisphosphonates on bone health in people with early and locally advanced breast cancer. A Cochrane review (O'Carrigan et al. 2017), 1 network meta-analysis ([Miyashita et al. 2020](#)) and 1 RCT ([Wilson et al. 2018](#)) reported on the effects of bisphosphonates on fractures. There was mixed evidence on the effectiveness of bisphosphonates at reducing fractures (either no evidence of effect or some evidence of effect). However evidence from 2 systematic reviews with meta-analyses ([Bassatne et al. 2022](#) and [Mei et al. 2020](#)), 1 network meta-analysis (Miyashita et al. 2020) and 1 RCT ([Kyvernitakis et al. 2018](#)) reporting on the effects of bisphosphonates on bone mineral/mass density indicate that bisphosphonate use is associated with significantly less bone loss compared with placebo or no treatment in people with early and

locally advanced breast cancer, thus supporting recommendation 1.9.6 on the use of bisphosphonate treatment for bone loss.

Other relevant NICE guidance

[Advanced breast cancer: diagnosis and treatment](#) (NICE guideline CG81) has [recommendations on bone metastases](#) which includes recommendation 1.5.14 to ‘consider offering bisphosphonates to patients newly diagnosed with bone metastases to prevent skeletal-related events and reduce pain’ and recommendation 1.5.15 which says ‘the choice of bisphosphonate for patients with bone metastases should be a local decision, taking into account patient preference and limited to preparations licensed for this indication.’ Within this exceptional review evidence for people with breast cancer and bone metastases was excluded as this is secondary breast cancer, as such the evidence we have reviewed does not impact on the recommendations on bisphosphonates for bone metastases within NICE guideline CG81.

Topic expert feedback

For this exceptional review we contacted 7 topic experts who were members of the guideline development group (GDG) for the NICE guideline NG101 or recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty and had an interest in breast cancer. Three topic experts responded: a consultant clinical oncologist, a consultant histopathologist and a specialist breast cancer pharmacist.

Two of the topic experts agreed with the proposal not to update.

One topic expert thought that the recommendations on adjuvant bisphosphonate treatment should be updated to consider changes in practice in relation to checking vitamin D levels before a patient starts bisphosphonates, and on the use of calcium and/or vitamin D with IV bisphosphonates. Details concerning tests and monitoring of treatments are not provided in NICE guideline recommendations as it is expected that healthcare professionals will check resources such as the British National

Formulary (BNF) for this information as standard practice. Under the BNF's monitoring requirements, it specifies that,

- for sodium clodronate, to monitor renal function, serum calcium and serum phosphate before and during treatment,
- for zoledronic acid, to “correct disturbances of calcium metabolism (e.g. vitamin D deficiency, hypocalcaemia) before starting. Monitor serum electrolytes, calcium, phosphate and magnesium”.

For sodium clodronate, the BNF also says under [directions for administration](#) that the “manufacturer advises avoid food or fluids (other than plain water) for 2 hours before and 1 hour after treatment, particularly calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids; maintain adequate fluid intake.” We will feedback to the BNF that information could be clearer about checking both calcium and vitamin D levels before initiating treatment and on taking these supplements whilst on bisphosphonate treatment.

This topic expert also said that a cross-reference to the NHS [PREDICT](#) breast cancer online tool could be added to recommendations on adjuvant bisphosphonate therapy, as it is designed to help patients and clinicians see how different treatments for early invasive breast cancer, including bisphosphonates, might improve survival rates after surgery according to the prognostic features of the disease. However NICE guideline NG101, [recommendation 1.6.8](#) on adjuvant therapy planning already recommends using the PREDICT tool “to estimate prognosis and the absolute benefits of adjuvant therapy for women with invasive breast cancer”.

The topic expert also said that they thought that the recommendations could be improved by clarifying approaches to adjuvant bisphosphonate therapy in patients who go through an early menopause due to chemotherapy. The recommendations refer to “postmenopausal women”, without describing whether the menopause is treatment-induced or ‘natural’. We will seek the views of stakeholders on whether this requires clarification.

As the current recommendations on adjuvant bisphosphonate therapy in NICE guideline NG101 do not provide details on the duration of adjuvant bisphosphonate or frequency of administration of zoledronic acid, topic experts were asked whether this causes any issues for clinical practice. All topic experts responded that this does not cause any practice issues.

In response to being asked about discrepancies between the recommendations on adjuvant bisphosphonates in NICE guideline NG101 and guidelines produced by other organisations, 1 topic expert highlighted that the American Society of Clinical Oncology-Ontario Health (Cancer Care Ontario) (ASCO-OH (CCO)) 2022 guideline on the [use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer](#) includes oral Ibandronate as an option, along with oral clodronate and IV zoledronic acid for postmenopausal (natural or induced) patients with nonmetastatic breast cancer, irrespective of hormone receptor and HER2 status. The recommendation by ASCO-OH (CCO) to include oral Ibandronate was based on interpretation by an expert panel of the findings of the Gralow et al. 2020 S0307 RCT that triggered this exceptional review. The study was identified from a systematic review which also included phase 3 RCTs or meta-analyses of adjuvant bisphosphonates and other bone-modifying agents used in the adjuvant treatment of primary, nonmetastatic breast cancer published between January 2016 and January 2021. Three other studies were included, 1 on IV zoledronic acid ([Friedl et al, 2021](#)) and 2 on [denosumab](#), which is not a bisphosphonate, and therefore not relevant to this surveillance review. The Friedl et al. 2021 study was identified in the focused literature search for this surveillance review but was excluded as it is on the optimal duration and schedule of administration of IV zoledronic acid (5 years versus 2 years of treatment). The “clinical interpretation” section in the ASCO-OH (CCO) 2022 guideline of the Gralow et al. 2020 study reports the same limitations identified in this surveillance review (see [discussion](#)).

Equalities

No equalities issues were identified during the surveillance process.

Decision proposal

Based on the new evidence it is proposed that NICE guideline NG101 is not updated in relation to the use of adjuvant bisphosphonates for early and locally advanced breast cancer. Overall, the evidence supports recommendations 1.9.1 and 1.9.2 to offer zoledronic acid or sodium clodronate as adjuvant therapy to postmenopausal women with node-positive breast cancer and to consider these bisphosphonates for patients with node-negative invasive breast cancer and a high risk of recurrence. The new evidence also reinforces what was already known about the risk of osteonecrosis of jaw from bisphosphonate treatment, with the greatest risk from IV zoledronic acid; and evidence supported previous findings that bisphosphonates are associated with improvements in bone health.

While we are aware of American guidance that recommends oral ibandronate for postmenopausal patients with nonmetastatic breast cancer, we consider that the evidence from 3 studies reporting on data from 2 RCTs on adjuvant ibandronate does not provide sufficient good quality evidence to support considering this bisphosphonate as an alternative treatment, as while the S0307 RCT found no differences between zoledronic acid, clodronate and ibandronate in survival outcomes for patients with stage I-III breast cancer, the limitations of the study (as described above) mean this is not sufficient to trigger an update. The study that analysed the data on osteonecrosis of the jaw in people participating in the S0307 RCT indicates that clodronate may be preferred over ibandronate as clodronate was associated with a significantly longer time to developing osteonecrosis of the jaw compared with ibandronate (or zoledronic acid). Additionally, the only other RCT evidence on ibandronate did not support its use in a specific population of patients with breast cancer (postmenopausal women with oestrogen receptor positive stage I to III breast cancer).

With regards to the recommendation for research on which groups of people with early and locally advanced breast cancer would benefit from the use of adjuvant bisphosphonates, we have noted that there is retrospective evidence from 2 RCTs that indicates MAF status may predict the likelihood of benefit

from adjuvant zoledronic acid and sodium clodronate in patients with early and locally advanced breast cancer, with outcomes differing between people with MAF-positive and MAF-negative tumours, and may also differ according to menopausal status. We will keep track of emerging prospective evidence on MAF diagnostic testing and evidence on whether it can predict outcomes in people with early and locally advanced breast cancer on adjuvant bisphosphonates.