NICE advice

Early breast cancer (preventing recurrence and improving survival): adjuvant bisphosphonates

Evidence summary
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Key points

The content of this evidence summary was up-to-date in July 2017. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Regulatory status: Bisphosphonates reduce the rate of bone turnover. Six bisphosphonates are available in the UK (alendronic acid, ibandronic acid, pamidronate, risedronate, clodronate and zoledronic acid), which have various indications. Bisphosphonates may be used in some people with breast cancer, within the terms of their licenses, to prevent and treat osteoporosis or skeletal events, or manage osteolytic lesions, bone pain or hypercalcaemia of malignancy. However, these treatments are not licensed for preventing recurrence or improving survival in people with early breast cancer, and use for this indication is off-label.

Overview

This evidence summary discusses a meta-analysis of individual participant data from 26 randomised controlled trials (RCTs) including 18,766 women with early breast cancer (the Early Breast Cancer Trialists' Collaborative Group [EBCTCG] meta-analysis 2015). The meta-analysis found that, at 10 years compared with control, adjuvant bisphosphonates (in addition to standard breast cancer treatments) produced small, borderline statistically significant reductions in distant recurrence (recurrence in the bone or elsewhere, not in the breasts or regional lymph nodes), bone

recurrence and breast cancer mortality (absolute reductions 1.4%, 1.1% and 1.7% respectively), but not breast cancer recurrence or all-cause mortality.

When prespecified subgroup analyses according to menopausal status were undertaken, no benefits were seen in premenopausal women, but the benefits in postmenopausal women were found to be greater than in the general study population. At 10 years compared with control, the absolute reductions in the risk of breast cancer mortality, bone recurrence and all-cause mortality in postmenopausal women were 3.3%, 2.2% and 2.3%, respectively.

The Cancer Care Ontario and the American Society of Clinical Oncology (CCO/ASCO) guideline on the Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer states that, although the EBCTCG meta-analysis found bisphosphonate treatment reduced the risk of bone recurrence and subsequently improved survival in postmenopausal women with early breast cancer, the absolute benefits were small compared with control and may not result in a clinically meaningful effect. Nevertheless, a Lancet comment accompanying the EBCTCG meta-analysis notes that the absolute reduction in the risk of dying from breast cancer among postmenopausal women (3.3% at 10 years) seen in the meta-analysis is similar to the benefit seen with anthracycline polychemotherapy versus nonanthracycline polychemotherapy.

The meta-analysis has limitations, primarily because the methods used were poorly reported. For example, there is no information on how trials were identified, no assessment of trial quality or risk of bias, no citations for publications for the included and excluded trials, and no indication whether the populations and treatments studied were homogeneous or not. It is also unclear what standard treatments were used for breast cancer in the included trials, whether standard treatment differed between pre- and postmenopausal women, and whether the treatments used reflect current clinical practice. Combining the data for all bisphosphonates in the meta-analysis was controversial, as was including small trials not designed to measure the outcomes of interest and performing a meta-analysis of subgroups. See the evidence strengths and limitations section of this evidence summary for more details.

The results of the meta-analysis suggest that bisphosphonates may be beneficial in postmenopausal women and provide an estimate of the average effects of bisphosphonates across the whole subgroup. However, evidence is insufficient to determine precise subgroups of postmenopausal women who would or would not benefit. The authors of the CCO/ASCO guideline note that the benefits might be less in women with low-risk cancers, which might be a factor in deciding whether to use treatment, particularly when balanced against the risk of adverse events with bisphosphonates. Similarly, more than half of the experts involved in developing European consensus guidance on adjuvant bisphosphonates for early breast cancer considered that

bisphosphonates should be used only in postmenopausal women at intermediate- or high-risk of recurrence of cancer.

Several decision-making tools such as Adjuvant! Online, PREDICT and the Nottingham Prognostic Index are available to help estimate the risk of recurrence and mortality, and the benefits of standard adjuvant treatments based on various clinical parameters. According to the CCO/ASCO guideline, similar parameters may be relevant when deciding whether or not bisphosphonates should be used. If treatment with bisphosphonates is considered appropriate, it should be discussed with each woman, taking their individual risk of recurrence and death into account and balancing this against their risk of adverse effects from bisphosphonates.

The optimal choice, dosage and duration of bisphosphonate treatment for preventing recurrence and improving survival in women with early breast cancer is unclear. Based on the evidence from the meta-analysis, the CCO/ASCO guideline generally recommends intravenous zoledronic acid (4 mg every 6 months for 3–5 years) or oral clodronate (1,600 mg daily for 2–3 years) for postmenopausal women with breast cancer deemed candidates for adjuvant bisphosphonate therapy (in addition to standard breast cancer treatments). The European consensus guideline also recommends 6-monthly intravenous zoledronic acid or daily oral clodronate for preventing metastases and improving disease outcomes in postmenopausal women with early breast cancer. There is less evidence to support the use of monthly intravenous zoledronic acid and daily oral ibandronic acid, and little or no evidence to support the use of risedronate and alendronic acid.

Different adverse effect profiles, frequency and route of administration, and cost may affect the choice of treatment. The EBCTCG meta-analysis did not report adverse effects, but the adverse effects of bisphosphonates are well-established. An older Cochrane review that considered the use of bisphosphonates in a broader population with breast cancer concluded that the adverse effects of bisphosphonates were generally mild and infrequent. Serious, rare adverse events associated with bisphosphonates include serious oesophageal reactions, osteonecrosis of the jaw, atypical stress fractures and renal impairment. The MHRA has issued guidance on preventing and managing these.

Results from ongoing trials may provide more evidence on the effects of bisphosphonates on breast cancer recurrence and survival in premenopausal women, allow more stable estimates of the 10-year outcomes in postmenopausal women, and provide comparisons of different bisphosphonate regimens.

A summary to inform local decision-making is shown in table 1.

Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications

Effectiveness

- In all women in the EBCTCG meta-analysis (n=18,766), the absolute 10-year risk with bisphosphonates compared with control was reduced by:
  - 1.4% for distant recurrence (20.4% compared with 21.8%, p=0.03)
  - 1.1% for bone recurrence (7.8% compared with 9.0%, p=0.004), and
  - 1.7% for breast cancer mortality (16.6% compared with 18.4%, p=0.04).

There was no statistically significant reduction in the risk of all-cause mortality or all breast cancer recurrence.

- A subgroup analysis found that in postmenopausal women (n=11,767) the absolute 10-year risk with bisphosphonates compared with control was reduced by:
  - 3.0% for breast cancer recurrence (22.8% compared with 25.8%, p=0.002)
  - 3.4% for distant recurrence (17.9% compared with 21.2%, p=0.0003)
  - 2.2% for bone recurrence (6.6% compared with 8.8%, p=0.0002) and
  - 3.3% for breast cancer mortality (14.7% compared with 18.0%, p=0.002)
  - 2.3% for all-cause mortality (21.1% compared with 23.5%, p=0.005).
- Bisphosphonate use had no statistically significant effect on distant recurrence other than bone recurrence, or on locoregional recurrence (in the same site as the original tumour or in the regional lymph nodes) or contralateral breast cancer (in the opposite breast).
- Subgroup analyses suggested that benefits were independent of the type and dosage of bisphosphonate, the tumour characteristics and the use of concomitant chemotherapy. No subgroup analyses assessed bisphosphonates according to women's estimated risk of breast cancer recurrence or mortality.

Safety

- Common adverse effects include gastrointestinal effects (such as nausea, dyspepsia, mild oesophagitis and abdominal pain) and bone, joint or muscle pain. Adverse effects vary among bisphosphonates, and some are related to the method of administration. See the individual summaries of product characteristics for more information.
- In 12 trials (n=10,124) in early breast cancer included in the Cochrane review, the incidence of osteonecrosis of the jaw was found to be from 0% to 0.7%.
- The MHRA has issued guidance on the use and safety of bisphosphonates, which summarises important safety issues with bisphosphonates, including oesophageal reactions, osteonecrosis of the jaw, atypical femoral fractures and adverse effects on renal function. The MHRA has also warned that osteonecrosis of the external auditory canal has been reported very rarely with bisphosphonates.

Patient factors

- Some people with breast cancer will be eligible for bisphosphonate treatment according to the licensed indications; for example, to reduce the risk of osteoporosis associated with aromatase inhibitors or chemotherapy-induced premature menopause (see the NICE guideline on early and locally advanced breast cancer: diagnosis and treatment).
- No information is available on adjuvant bisphosphonates for preventing recurrence or improving survival in men with early breast cancer.
- The optimal choice, dosage and duration of bisphosphonate treatment for preventing recurrence and improving survival is unclear. Most trials included in the meta-analysis lasted 2–5 years.
- The bisphosphonates used most commonly in the trials were zoledronic acid (50%), clodronate (27%) and ibandronic acid (16%). There is little or no evidence to support the use of risedronate, alendronic acid or pamidronate for preventing recurrence and improving survival in people with early breast cancer.
- Although serious adverse effects are rare, they should be discussed with women considering adjuvant bisphosphonate therapy and measures should be taken to reduce the risk of them occurring (see the MHRA guidance).
- Oral bisphosphonates such as clodronate are more likely to cause gastrointestinal adverse effects than intravenous bisphosphonates and some people may find them difficult to swallow. Nevertheless, some people may prefer oral medication because a hospital visit is not required.
- Zoledronic acid is administered intravenously and, it may be easier for some people to adhere to 6-monthly intravenous treatment, rather than daily oral treatment. Zoledronic acid infusion can cause an acute response resulting in flu-like symptoms.
- Calcium and vitamin D supplementation is generally recommended when bisphosphonates are used, particularly if dietary intake is low.

Resource implications

- The annual cost (excluding VAT) of zoledronic acid given at the dosages generally used in the meta-analysis ranges from around £8 to £47. Clodronate costs around £1780 per year and ibandronic acid costs around £80 per year (costs taken from Drugs and pharmaceutical electronic market information and the Drug Tariff; excluding VAT). These costs do not include any local procurement discounts or other costs incurred, such as dilution and administration, standard supportive therapy (such as calcium and vitamin D), or any costs associated with attendance for day case treatment.
- Depending on the bisphosphonate used, additional costs that need to be considered include dental check-ups and monitoring of renal function and vitamin D levels (see the MHRA guidance).
- It is unclear how many additional appointments and investigations will be required with bisphosphonate treatment on top of those required for standard management of breast cancer. It is also unclear what savings might be seen as a result of such treatment; for example, due to a reduction in the need for dual energy X-ray absorptiometry (DEXA) scans in people taking breast cancer treatments that are associated with osteoporosis, or by reducing the number of people needing treatment for metastatic disease.

Introduction and current guidance

Breast cancer is the most common cancer in women in England and Wales, and also occurs rarely in men. Most breast cancers are diagnosed at an early stage, when all detected deposits of the disease are in the breast or nearby lymph nodes and can be removed surgically. Early breast cancer is subdivided into 2 major categories, in situ disease and invasive cancer. Although most women with early breast cancer now survive, some have undetected deposits of cancer cells remaining after surgery in or near the breast, or at distant sites (for example, in bone). These can start to proliferate, sometimes many years later, resulting in a recurrence of the original breast cancer. Therefore, adjuvant treatments may be given in addition to surgery for early breast cancer to try to kill any remaining cancer cells (NICE guideline on early and locally advanced breast cancer: diagnosis and treatment and EBCTCG: Early Breast Cancer Trialists' Collaborative Group).

The NICE guideline on early and locally advanced breast cancer covers diagnosis and surgical and pharmacological treatment of women and men with early and locally advanced breast cancer (currently being updated). An interactive flowchart brings together everything NICE has published on this subject.

In women treated for breast cancer, aromatase inhibitors and chemotherapy-induced premature menopause are associated with osteoporosis, which increases the risk of bone fractures. Therefore, NICE guidance on early breast cancer recommends that people with early invasive breast cancer should have a baseline dual energy X-ray absorptiometry (DEXA) scan to assess bone mineral density if they:

- are starting adjuvant aromatase inhibitor treatment
- are starting ovarian ablation or suppression therapy
- have treatment-induced menopause.

Bisphosphonates should be offered to women identified by the algorithms in Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK expert group (see appendix 2 of NICE's full guideline).

The NICE guideline on advanced breast cancer recommends that bisphosphonates should also be considered for people newly diagnosed with bone metastases to prevent skeletal adverse events and reduce pain.

Bisphosphonates may also have a role in the prevention of metastatic disease. It has been hypothesised that, in bone with high turnover, excess osteoclast activity could be associated with excess production of growth factors, which could in turn affect the survival of tumour micrometastases. Using bisphosphonates to reduce osteoclast activity might reduce expression of these factors, thereby preventing the establishment of micrometastatic disease. However, RCTs examining this possible effect have found mixed results (Brufsky and Mathew 2015).This evidence summary considers the best available evidence for using bisphosphonates off-label as adjuvant treatments for early breast cancer, to prevent recurrence and improve survival, rather than for their licensed indications, such as treating or preventing osteoporosis or skeletal events, or managing bone pain.

Product overview

Mode of action

Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone, slowing their rate of growth and dissolution, and inhibiting osteoclast maturation and function, thereby reducing the rate of bone turnover (British national formulary, March 2017, Brufsky and Mathew 2015).

Regulatory status

Six bisphosphonates are available in the UK: alendronic acid (alendronate sodium), ibandronic acid (ibandronate sodium), pamidronate disodium, risedronate sodium, sodium (and disodium) clodronate and zoledronic acid (zoledronate).

The following list shows some of the licensed indications and usual dosages for bisphosphonates, focussing on those that are most relevant to the population included in this evidence summary. Other licensed indications for bisphosphonates include management of osteoporosis in men, corticosteroid-induced osteoporosis, hypercalcaemia of malignancy and Paget's disease. The medicines are administered orally, unless stated otherwise. Where a treatment frequency or duration is not stated, a single dose is used. See the summaries of product characteristics or British national formulary for more detailed information on the licensed indications and dosages for individual bisphosphonates.

- Treating osteoporosis in postmenopausal women:
    - alendronic acid 10 mg daily or 70 mg weekly
    - ibandronic acid 150 mg monthly or 3 g intravenously (IV) every 3 months
    - risedronate sodium 5 mg daily or 35 mg weekly
    - zoledronic acid 5 mg IV yearly.
- Preventing skeletal events in people with breast cancer and bone metastases:
    - ibandronic acid 50 mg daily or 6 mg IV every 3–4 weeks
    - zoledronic acid 4 mg IV every 3–4 weeks.
- Managing osteolytic lesions and bone pain in people with breast cancer or multiple myeloma and bone metastases:
    - pamidronate disodium 90 mg IV every 4 weeks
    - sodium clodronate 1,600 mg daily.

Bisphosphonates may be used in some people with breast cancer, within the terms of their licenses, to prevent osteoporosis or skeletal events, or manage osteolytic lesions, bone pain or hypercalcaemia of malignancy. However, these treatments are not licensed for preventing recurrence or improving survival in people with early breast cancer, and use for this indication is

off-label. In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the patient and whether using bisphosphonates is suitable outside its authorised indications. Supporting information and advice is also available from the GMC.

Dosing information

Dosing information varies for the licensed indications for the bisphosphonates and, although the usual dosages are briefly listed above, more detail can be found in the summaries of product characteristics.

Dosing information for bisphosphonates for adjuvant use to prevent recurrence and improve survival in people with early breast (off-label indication) is discussed in the estimated impact for the NHS section of this evidence summary.

Cost

Table 2 lists a range of costs for the 6 bisphosphonates at the usual dosages covering most of the licensed indications. Dosages shown do not represent the full range that can be used and do not imply therapeutic equivalence. The costs shown are for 4 weeks' treatment, unless the bisphosphonate is generally administered as a single dose.

The costs shown for IV treatments do not cover the full range of available products. Also, costs are for the medicines only (excluding VAT) and do not include any local procurement discounts or other costs incurred, such as dilution and administration, standard supportive therapy (such as calcium and vitamin D), or any costs associated with attendance for day case treatment.

Table 2 Costs of bisphosphonates

Medicine	Dosage[a] and quantity	Cost per 28 days or single dose, as indicated, excluding VAT
Alendronic acid	10 mg daily x 28 tablets	£1.69[b]
	70 mg weekly x 4 tablets	£0.72[b]
Ibandronic acid	50 mg daily x 28 tablets	£6.27[b]
	150 mg monthly x 1 tablet	£1.13[b]

	1 mg/ml x 2 ml vial x 1 single dose	£23.26[c]
	1 mg/ml x 3 ml syringe x 1 single dose	£10.27[c]
Pamidronate disodium	9 mg/ml x 10 ml vial x 1 single dose	£4.10[c]
Risedronate sodium	5 mg daily x 28 tablets	£18.85[b]
	35 mg weekly x 4 tablets	£0.85[b]
Sodium clodronate	1,600 mg daily, 800 mg x 56 tablets	£136.67[b]
Zoledronic acid	5 mg/100 ml bag x 1 single dose	£7.36[c]
	4 mg/100 ml bag x 1 single dose	£3.94[c]

[a] Dosages are taken from the relevant SPCs. Those shown do not represent the full range that can be used and do not imply therapeutic equivalence

[b] Costs taken from the Drug Tariff, June 2017; excluding VAT

[c] Average price paid in English NHS hospital trusts over the last 4 months of 2015 taken from Drugs and pharmaceutical electronic market information; excluding VAT

Evidence review

This evidence summary includes the best available evidence to support the off-label use of adjuvant bisphosphonates to prevent recurrence and improve survival in people with early breast cancer. A literature search was conducted which identified 89 references (see search strategy for full details). These references were screened using their titles and abstracts and 6 references were obtained and assessed for relevance.

One study was included in this evidence summary, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis (2015). A summary of this study is shown in the table below (see evidence tables for full details).

Table 3 Summary of included study

Study	Population	Intervention and comparison	Primary outcomes
EBCTCG 2015 Meta-analysis of individual participant data from 26 RCTs[a]	18,766 women[a] with early breast cancer (not defined)	Adjuvant bisphosphonate treatment (mainly zoledronic acid 50%, clodronate 27% and ibandronic acid 16%) compared with no bisphosphonate treatment (including placebo)	Recurrence of breast cancer Distant recurrence of cancer[b] Breast cancer mortality
[a] 11,767 women were postmenopausal, 6171 women were premenopausal and 828 women were perimenopausal [b] Recurrence in the bone or elsewhere, not in the breasts or regional lymph nodes			
Abbreviations: EBCTCG, Early Breast Cancer Trialists' Collaborative Group; RCT, randomised controlled trial			

The remaining 5 references were excluded and are listed in excluded studies with reasons for their exclusion. They include a 2012 Cochrane review that assessed the effects of bisphosphonates and other bone agents for breast cancer (including 12 RCTs in early breast cancer, n=10,124), which has been superseded by the EBCTCG meta-analysis.

Clinical effectiveness

Of 18,766 women included in the EBCTCG meta-analysis (2015), over a median follow-up of 5.6 woman-years, breast cancer recurred in 3,453 women (18.4%), after which 2,106 women (11.2%) died. Overall, use of bisphosphonates compared with control resulted in no statistically significant reduction in the recurrence of breast cancer, but there were statistically significant reductions in distant recurrence (mainly because of a reduction in bone recurrence) and breast cancer mortality. With bisphosphonates compared with control, the absolute 10-year risk was reduced by:

- 1.1% for breast cancer recurrence (24.9% compared with 25.9%; rate ratio [RR] 0.94, 95% confidence interval [CI] 0.87 to 1.01; p=0.08, not statistically significant)

- 1.4% for distant recurrence (20.4% compared with 21.8%; RR 0.92, 95% CI 0.85 to 0.99; p=0.03)
- 1.1% for bone recurrence (7.8% compared with 9.0%; RR 0.83, 95% CI 0.73 to 0.94; p=0.004), and
- 1.7% for breast cancer mortality (16.6% compared with 18.4%; RR 0.91, 95% CI 0.83 to 0.99; p=0.04)
- 1.6% for all-cause mortality (20.8% compared with 22.3%; RR 0.92, 95% CI 0.85 to 1.00, p=0.06, not statistically significant).

In the prespecified subgroup analyses (which may have been post-hoc for the individual trials included in the meta-analysis), no statistically significant benefits from bisphosphonate use were seen in premenopausal women (n=6,171) compared with control. In postmenopausal women (n=11,767, natural or induced menopause), there were statistically significant reductions in breast cancer recurrence, distant recurrence (recurrence in the bone or elsewhere, not in the breasts or regional lymph nodes), bone recurrence and breast cancer mortality. The absolute reductions with bisphosphonates compared with control in postmenopausal women at 10 years were:

- 3.0% for breast cancer recurrence (22.8% compared with 25.8%; RR 0.86, 95% CI 0.78 to 0.94; p=0.002)
- 3.4% for distant recurrence (17.9% compared with 21.2%; RR 0.82, 95% CI 0.74 to 0.91; p=0.0003)
- 2.2% for bone recurrence (6.6% compared with 8.8%; RR 0.72, 95% CI 0.60 to 0.86; p=0.0002) and
- 3.3% for breast cancer mortality (14.7% compared with 18.0%; RR 0.82, 95% CI 0.73 to 0.93; p=0.002)
- 2.3% for all-cause mortality (21.1% compared with 23.5%; RR 0.86, 95% CI 0.77 to 0.96, p=0.005).

Bisphosphonate use had no statistically significant effect on distant recurrence other than bone recurrence, or on locoregional recurrence (in the same site as the original tumour or in the regional lymph nodes) or contralateral breast cancer (in the opposite breast) in all women or in the postmenopausal subgroup.

Subgroup analyses looking at bone recurrence and breast cancer mortality suggested that the efficacy of bisphosphonates is greater in women aged 55 years or older, compared with younger women. However, menopausal status and age are closely correlated so it is difficult to know which characteristic is most relevant. Reductions in bone recurrence and breast cancer mortality did not depend on tumour characteristics (including oestrogen receptor status, nodal status or tumour grade). No subgroup analyses assessed bisphosphonates according to women's estimated risk of breast cancer recurrence or mortality.

No statistically significant difference was found between non-aminobisphosphonates (clodronate) and aminobisphosphonates (zoledronic acid and ibandronic acid). There was no apparent benefit with the non-aminobisphosphonate pamidronate (taken orally), but the number of women taking this bisphosphonate was low (n=953) and so the meta-analysis may have had insufficient statistical power to detect a benefit. The number of women taking risedronate (n=398) was also low and insufficient to assess its efficacy, and no women received alendronic acid or intravenous (IV) pamidronate in the trials included in the meta-analysis.

For bone recurrence, there was no statistically significant difference between low-intensity bisphosphonate schedules (such as 6-monthly IV zoledronic acid) and high-intensity schedules (such as monthly IV zoledronic acid, daily oral ibandronic acid or daily oral clodronate). Similar reductions with bisphosphonates were seen in the presence or absence of chemotherapy, suggesting any benefits are additive to chemotherapy.

An overview of the key results for clinical effectiveness can be found in results tables.

Safety and tolerability

The most common adverse effects of bisphosphonates are gastrointestinal effects (such as nausea, dyspepsia, mild oesophagitis and abdominal pain) and bone, joint or muscle pain. Other less common adverse effects include more serious oesophageal reactions (such as oesophagitis and oesophageal ulcers, strictures and erosions), osteonecrosis of the jaw and atypical stress fractures (NICE clinical knowledge summaries on osteoporosis - prevention of fragility fractures). Adverse effects vary among bisphosphonates. See the individual summaries of product characteristics (SPCs) for more information.

The EBCTCG meta-analysis (2015) did not report adverse effects. The bisphosphonates used most commonly in the trials in the meta-analysis were oral clodronate and IV zoledronic acid. Adverse effects reported in between 1 in 10 and 1 in 100 people taking sodium clodronate for the licensed indications are asymptomatic hypocalcaemia, diarrhoea, nausea, vomiting and increased

transaminases (within the normal range) (Bonefos SPC). Adverse effects reported in between 1 in 10 and 1 in 100 people taking zoledronic acid 4 mg for the licensed indications are anaemia, headache, conjunctivitis, nausea, vomiting, decreased appetite, bone pain, myalgia, arthralgia, generalised pain, renal impairment, fever, flu-like syndrome, increased blood creatinine and urea, and hypocalcaemia. Hypophosphataemia occurs in more than 1 in 10 people taking zoledronic acid (Zometa SPC).

A 2012 Cochrane review of 34 randomised controlled trials (RCTs) that assessed the effects of bisphosphonates and other bone agents for breast cancer (including 12 RCTs in early breast cancer, n=10,124) reported adverse events. It concluded that the adverse effects of bisphosphonates were generally mild and infrequent. The main adverse effect seen with IV zoledronic acid was renal toxicity, which was related to the dose and infusion time. No significant renal toxicity was seen with IV pamidronate or IV ibandronic acid. The main adverse effect seen with oral clodronate and oral ibandronic acid was mild gastrointestinal toxicity. The authors noted that there have been reports of osteonecrosis of the jaw with long-term use of bisphosphonates. In the trials in early breast cancer included in the Cochrane review, the incidence of osteonecrosis of the jaw was found to be from 0% to 0.7%, highlighting the need for good oral care before and during treatment in people taking bisphosphonates long-term.

The MHRA has issued guidance on the use and safety of bisphosphonates, which summarises important safety issues with bisphosphonates, including oesophageal reactions, osteonecrosis of the jaw, atrial fibrillation, atypical femoral fractures and adverse effects on renal function. Since this was published in 2014, the MHRA has also warned that osteonecrosis of the external auditory canal has been reported very rarely with bisphosphonates.

Evidence strengths and limitations

The EBCTCG meta-analysis (2015) was a large, meta-analysis of individual participant data from RCTs. Of the 32 trials (n=19,291) identified that recorded recurrence, data were not obtained for 6 trials; however, these included only 525 women and would have been unlikely to change the key outcomes of the meta-analysis. Data were obtained for 26 trials (n=18,766, 97% of participants). Citations for publications for the included and excluded trials were not reported.

The methods of identifying trials, seeking collaboration, data collection, collation, checking, and presentation have not been fully reported, apart from to note these were undertaken as in previous EBCTCG reports. In addition, no assessment of quality or risk of bias of the individual trials is provided, including randomisation, allocation concealment, blinding and adjudication of outcomes. Most of the trials included in the meta-analysis were open-label; outcome assessment was often

not blinded (although this will have limited effect on measures of recurrence and survival); and some of the trials were industry-sponsored. The subgroup analyses in the EBCTCG meta-analysis were prespecified, but may not have been prespecified in the individual trials: details are not reported.

The paper does not report if the populations and treatments studied were homogeneous. For example, it is unclear whether differences in the standard breast cancer management of pre- and postmenopausal women may account for the differences in benefits in these populations, rather than bisphosphonates. It is also unclear what chemotherapy was used for breast cancer, whether it was similar across the trials, and whether choice of chemotherapy reflects current clinical practice. Breast cancer survival has improved significantly over the last few decades because of better treatments and better identification of risk groups. It is possible that bisphosphonates only benefited women who had suboptimal treatment in the older trials. Nevertheless, the 2 largest trials included in the EBCTCG meta-analysis, the ABCSG-12 (n=1,083) and AZURE (BIG 01/04) trials (n=3,360) enrolled participants until 2006, and sensitivity analyses excluding these trials still found benefits of bisphosphonates in postmenopausal women.

Overall, the authors of the Cancer Care Ontario and the American Society of Clinical Oncology (CCO/ASCO) guideline on the Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer considered that the EBCTCG had strict inclusion criteria and protocols and the results of the EBCTCG meta-analysis are of high-quality, with the limitation that some outcomes have not yet been completely reported. However, they highlighted that combining the data for all bisphosphonates in the meta-analysis was controversial, as was including small trials not designed to measure the outcomes of interest; for example, some trials were designed to look at bone mineral density and did not report recurrence or survival. This also means that there may have been no adjudication of these outcomes in those trials. Furthermore, it has been questioned whether a meta-analysis of subgroups should be used to inform clinical decision making because subgroup analyses are prone to error and generally considered more appropriate for hypothesis generation for future trials than changing practice (Jacobs et al. 2015).

The EBCTCG used log-rank statistics to assess the effects of bisphosphonates compared with control on various outcomes, and to estimate rate ratios and their confidence intervals. Log-rank analyses allow analyses of the effects of treatment in separate years, which may improve medical understanding but can also carry some statistical uncertainties. Estimates for a given year can only be based on trials that have follow-up and data reported in that year. The median follow-up in the meta-analysis was 5.6 years and the interquartile range was 3.7 years to 8.0 years. This means that 75% of women were followed up for 8 years or less. It is unclear how many women were followed up for 10 years but the number is likely to be low when subgroups are considered.

Although data on safety outcomes were reportedly collected, adverse effects were not reported in the EBCTCG meta-analysis; however, the adverse effect profile of bisphosphonates is well-established. The trials in the meta-analysis included women only and no information is available on using bisphosphonates to prevent recurrence of breast cancer in men. When considering menopausal status, women with natural menopause and premature menopause induced by chemotherapy or oophorectomy were included in the same subgroup. Only 1 trial (ABCSG-12, n=1,803), which studied zoledronic acid, included women with induced menopause. The majority of participants in the meta-analysis (83%) also received adjuvant chemotherapy, and bisphosphonate treatment generally started 0–12 weeks after surgery or chemotherapy. Clodronate has not been studied specifically in people receiving aromatase inhibitors (CCO/ASCO guideline).

Little or no information is available for some commonly used bisphosphonates, such as risedronate and alendronic acid. No benefit was seen with oral pamidronate but the authors of the meta-analysis note that this might be expected because the oral formulation is poorly absorbed and pamidronate has been shown to have little or no effect on markers of bone resorption, metastatic bone disease and myeloma. Only limited information from subgroup analyses is available comparing different bisphosphonates, or different dosages of bisphosphonates (low- or high-intensity schedules). Most of the participants (97%) were in trials lasting 2–5 years, and the optimal duration of treatment is unclear.

The authors of the meta-analysis note that more reliable comparisons of different bisphosphonate regimens may emerge from ongoing trials that compare them directly; for example, the SWOG 0307 trial (NCT00127205) comparing clodronate, zoledronic acid and ibandronic acid over 3 years (n=5,400), and the SUCCESS trial (NCT02181101) comparing 5 years' and 2 years' treatment with zoledronic acid (n=3,800). Results of an interim analysis from SWOG 0307 have been published as an abstract only, suggesting there were no significant differences between the groups in 5-year disease-free survival or overall survival, but there were some differences in adverse events (Gralow et al. 2015). Full publication of the trial is needed before the relevance of the results can be assessed.

A literature search was undertaken in June 2016 for the CCO/ASCO guideline on the use of adjuvant bisphosphonates and other bone-modifying agents in breast. In addition to trials of bisphosphonates with data included in the EBCTCG meta-analysis, the search found results for SWOG S0307 and a few small trials on clodronate and zoledronic acid. However, the authors noted that data on survival and recurrence were reported in abstracts only and that the results do not currently change the conclusions of the EBCTCG meta-analysis. Results from ongoing trials (including HOBOE [NCT00412022] and TEAM-IIb [ISRCTN17633610]), and longer follow-up of the trials included in the EBCTCG meta-analysis, may provide more evidence on the effects of

bisphosphonates in premenopausal women, and allow more stable estimates of the 10-year outcomes in postmenopausal women.

An overview of the quality assessment for the included study can be found in the evidence tables.

Estimated impact for the NHS

Other treatments

In the trials in the EBCTCG meta-analysis (2015), bisphosphonates were administered in addition to other treatments for breast cancer; for example, chemotherapy and surgery.

In the trials included in the meta-analysis, 9,290 women received zoledronic acid, 5,053 women received clodronate, 3,072 women received ibandronic acid, 953 women received pamidronate and 398 women received risedronate sodium. The bisphosphonates were usually administered at the following dosages, for the listed durations:

- intravenous (IV) zoledronic acid 4 mg 3- or 4-weekly or 6-monthly for 3–5 years (some trials used intermediate frequencies such as 3-monthly, or monthly for an initial period then 6-monthly)
- oral clodronate 1,600 mg daily for 2–3 years
- oral ibandronic acid 50 mg daily for 2 years
- oral pamidronate 150 mg twice daily for 4 years
- oral risedronate 35 mg weekly for 1–2 years.

Based on the evidence, the CCO/ASCO guideline generally recommends IV zoledronic acid (4 mg every 6 months for 3–5 years) or oral clodronate (1,600 mg daily for 2–3 years) for postmenopausal women with breast cancer deemed candidates for adjuvant bisphosphonate therapy (in addition to standard breast cancer treatments, and calcium and vitamin D supplementation). The lower dose of zoledronic acid is recommended because the EBCTCG meta-analysis found no statistically significant difference between less- and more-intensive dosage schedules in terms of bone recurrence, and adverse effects are less common and less severe with less-intensive regimens.

European consensus guidance on adjuvant bisphosphonates for early breast cancer also recommends that IV zoledronic acid (4 mg every 6 months) or oral clodronate (1,600 mg daily) are the preferred agents for preventing recurrence of breast cancer and improving disease outcomes.

The guideline states that the potential risks and benefits of 3–5 years of adjuvant bisphosphonate treatment (plus vitamin D supplementation and adequate calcium intake) should be discussed with relevant women.

Costs of bisphosphonates used most often in the meta-analysis

No cost-effectiveness studies were found considering bisphosphonates for preventing recurrence and improving survival in people with early breast cancer.

Table 4 shows the costs of bisphosphonates at the dosages most commonly used in the EBCTCG meta-analysis. The dosages shown do not represent the full range that can be used and they do not imply therapeutic equivalence. Oral pamidronate is not included in the table because the meta-analysis found it was ineffective and it is not currently available in the UK. Risedronate is not included because relatively few women took this medicine in the trials in the meta-analysis.

The costs shown in the table are for the medicines only (excluding VAT) and do not include any local procurement discounts or other costs incurred, such as dilution and administration, or any costs associated with attendance for day case treatment. Calcium and vitamin D supplementation is generally recommended when bisphosphonates are used, particularly if dietary intake is low; the cost of this is not included in the table.

Table 4 Annual costs of bisphosphonates commonly used in the EBCTCG meta-analysis

Medicine	Usual dosage	Cost per unit, excluding VAT	Annual cost, excluding VAT
IV zoledronic acid 4 mg/ 100 ml	4 mg monthly for 3–5 years	£3.94[b] per vial	£47.28
	4 mg 6-monthly for 3–5 years	£3.94[b] per vial	£7.88
Oral sodium clodronate 800 mg	1,600 mg daily for 2–3 years	£136.67[c] per 56 tablets	£1781.59
Oral ibandronic acid 50 mg	50 mg daily for 2 years	£6.27[c] per 28 tablets	£81.73

[a] The dosages shown reflect those most commonly used in the EBCTCG meta-analysis. They do not represent the full range that can be used and do not imply therapeutic equivalence

[b] Average price paid in English NHS hospital trusts over the last 4 months of 2015 taken from Drugs and pharmaceutical electronic market information; excluding VAT

[c] Costs taken from the Drug Tariff, April 2017; excluding VAT

It is unclear how many additional appointments and investigations will be required with bisphosphonate treatment on top of those required for standard management of breast cancer. It is also unclear what savings might be seen as a result of such treatment; for example, due to a reduction in the need for dual energy X-ray absorptiometry (DEXA) scans in people taking breast cancer treatments that are associated with osteoporosis (see the NICE guideline on early and locally advanced breast cancer: diagnosis and treatment), or by reducing the number of people with metastatic disease.

Current or estimated usage

Estimating the current usage off-label usage of bisphosphonates as adjuvant treatments for preventing the recurrence of early breast cancer and improving survival is difficult because bisphosphonates are used to treat various conditions. No information on prescribing adjuvant bisphosphonates for early breast cancer was available at the time this evidence summary was prepared.

Likely place in therapy

Local decision makers need to take safety, efficacy, cost and patient factors into account when considering the likely place in therapy of adjuvant bisphosphonates for preventing recurrence and improving survival in people with early breast cancer.

In the EBCTCG meta-analysis, in women with early breast cancer treated with adjuvant bisphosphonates, there were small, borderline statistically significant reductions in distant recurrence, bone recurrence and breast cancer mortality, but not breast cancer recurrence, at 10 years compared with control. No information is available on adjuvant bisphosphonates for preventing recurrence or improving survival in men with early breast cancer.

When prespecified subgroup analyses according to menopausal status were undertaken, no benefits were seen in premenopausal women, but the benefits were found to be higher than in the general study population for postmenopausal women. At 10 years compared with control, the

absolute reductions in the risk of breast cancer death and bone recurrence in postmenopausal women were 3.3% (14.7% compared with 18.0%; p=0.002; number needed to treat [NNT] 31) and 2.2% (6.6% compared with 8.8%; p=0.0002; NNT 46) respectively. Benefits appeared to be independent of the type and dosage of bisphosphonate, the tumour characteristics and the use of concomitant chemotherapy.

The CCO/ASCO guideline states that, although the EBCTCG meta-analysis found bisphosphonate treatment reduced the risk of bone recurrence and subsequently improved survival in postmenopausal women with early breast cancer, the absolute benefits were small compared with control and may not result in a clinically meaningful effect. Nevertheless, a Lancet comment accompanying the EBCTCG meta-analysis notes that the absolute reduction in the risk of dying of breast cancer (3.3% at 10 years) seen in the meta-analysis is similar to the benefit seen with anthracycline polychemotherapy versus nonanthracycline polychemotherapy.

The evidence is insufficient to determine precise subgroups of postmenopausal women who would or would not benefit. The authors of the CCO/ASCO guideline consider that the benefits of bisphosphonates might be less in women with low-risk cancers, which might be a factor in deciding whether to use treatment, particularly when balanced against the risk of adverse events with bisphosphonates. Similarly, when the European consensus guidance on adjuvant bisphosphonates for early breast cancer was developed, although the panel agreed that data supported the use of adjuvant bisphosphonates in postmenopausal (whether natural or induced) women, 58% of the experts (14/24) suggested restricting use to women considered at intermediate- or high-risk of recurrence of breast cancer rather than unselected use across all risk groups.

Several decision-making tools such as Adjuvant! Online, PREDICT and the Nottingham Prognostic Index are available to help estimate the risk of recurrence and mortality, and the benefits of standard adjuvant treatments based on various clinical parameters. According to the CCO/ASCO guideline, similar parameters may be relevant when deciding whether or not bisphosphonates should be used. If treatment with bisphosphonates is considered appropriate, it should be discussed with each woman, taking their individual risk of recurrence and death into account and balancing this against their risk of adverse effects from bisphosphonates.

The optimal choice, dosage and duration of bisphosphonate treatment for preventing recurrence and improving survival in women with early breast cancer is unclear. Based on the available evidence, the CCO/ASCO guideline generally recommends IV zoledronic acid (4 mg every 6 months for 3–5 years) or oral clodronate (1,600 mg daily for 2–3 years) for postmenopausal women with breast cancer deemed candidates for adjuvant bisphosphonate therapy (in addition to standard breast cancer treatments). The European consensus guideline also recommends 6-monthly IV

zoledronic acid or daily oral clodronate first-line for preventing metastases and improving disease outcomes in postmenopausal women with early breast cancer. There is less evidence to support the use of monthly IV zoledronic acid and daily oral ibandronic acid, and little or no evidence to support the use of risedronate and alendronic acid.

Different adverse effect profiles, frequency and route of administration, and cost may affect the choice of treatment. Adverse effects vary among bisphosphonates. Oral bisphosphonates such as clodronate are more likely to cause gastrointestinal adverse effects than IV bisphosphonates and some people may find them difficult to swallow. Nevertheless, some people may prefer oral medication because a hospital visit is not required. Zoledronic acid is administered intravenously and, it may be easier for some people to adhere to 6-monthly IV treatment, rather than daily oral treatment. Zoledronic acid infusion can cause an acute response resulting in flu-like symptoms. More serious, less common adverse events associated with bisphosphonates include serious oesophageal reactions, osteonecrosis of the jaw, atypical stress fractures and renal impairment. The MHRA has issued guidance on preventing and managing these.

The annual cost of zoledronic acid given at the dosages generally used in the meta-analysis ranges from around £8 to £47 (excluding VAT), not including any local procurement discounts or other costs incurred, such as dilution and administration, standard supportive therapy (such as calcium and vitamin D), or any costs associated with attendance for day case treatment. Clodronate costs around £1780 per year and ibandronic acid costs around £80 per year (excluding VAT).

Information for the public about medicines

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn't another suitable medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

Information about licensing of medicines

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients,

and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on NHS Choices.

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council's good practice guidelines. These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to decide whether or not to have the treatment. This is called giving informed consent.

Questions that might be useful to ask about medicines

- Why am I being offered this medicine?
- Why am I being offered a medicine that is unlicensed or is being used off-label?
- What does the treatment involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits?
- Could having the treatment make me feel worse?
- Are there other treatments I could try?
- What are the risks of the treatment?
- Are the risks minor or serious? How likely are they to happen?
- What could happen if I don't have the treatment?

Relevance to other NICE programmes

The use of adjuvant bisphosphonates for preventing recurrence and improving survival in early breast cancer is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has issued the following guidance relating to early breast cancer:

- Early and locally advanced breast cancer: diagnosis and treatment (2009) NICE guideline CG80, currently being updated
- Improving outcomes in breast cancer (2002) NICE guideline CSG1
- Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer (2006) NICE technology appraisal guidance 112
- Axxent electronic brachytherapy system for early stage breast cancer (2016) NICE medtech innovation briefing 76
- Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (2013) NICE diagnostics guidance 10.

A NICE interactive flowchart on early and locally advanced breast cancer and a quality standard on breast cancer (2011; updated 2016) are also available.

The following NICE guidance relates to licensed indications for bisphosphonates:

- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (2008) NICE technology appraisal guidance 160
- Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (2008) NICE technology appraisal guidance 161.

As well as guidance, NICE produces advice publications which do not constitute formal NICE guidance but critically appraise the evidence to help decision-making. These include:

- Early and metastatic HER2-positive breast cancer: subcutaneous trastuzumab (2013) NICE evidence summary ESNM13.

References

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Dhesy-Thind S, Fletcher GG, Blanchette PS et al (2017) Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology 35: 2062–81

Early Breast Cancer Trialists' Collaborative Group (2015) Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 386: 1353–61

Gnant M, Mlineritsch B, Stoeger H et al. (2015) Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: Final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. Annals of Oncology 26(2): 313–20

Gralow J, Barlow WE, Alexander HG et al. (2015) Phase III Trial of Bisphosphonates as Adjuvant Therapy in Primary Breast Cancer: SWOG/Alliance/ECOG-ACRIN/NCIC Clinical Trials Group/ NRG Oncology Study S0307. Journal of Clinical Oncology 33 (suppl; abstr 503)

Hadji P, Coleman RE, Wilson C et al. (2016) Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. Annals of Oncology 27(3): 379–90

Jacobs C, Amir E, Paterson A et al. (2015) Are adjuvant bisphosphonates now standard of care of women with early stage breast cancer? A debate from the Canadian Bone and the Oncologist New Updates meeting. Journal of Bone Oncology 4(2): 54–8

Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, et al. (2015) Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use. PLoS Med 12(7): e1001855

Wong MHF, Stockler MR and Pavlakis N. Bisphosphonates and other bone agents for breast cancer. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003474. DOI: 10.1002/ 14651858.CD003474.pub3

Evidence tables

Table 5 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2015)

Study reference	EBCTCG (2015) Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 386: 1353–61
Unique identifier	Not applicable
Study type	Meta-analysis of individual participant data from 26 RCTs
Aim of the study	To clarify whether adjuvant bisphosphonates reduce the risk of breast cancer recurring, breast cancer mortality, and of bone and other metastases. Also, whether menopausal status affects efficacy in women with early breast cancer
Study dates	Trials were eligible if they began before 2008. Information on individual participants was sought between 2012 and 2014
Setting	The trials in the meta-analysis were undertaken worldwide, including the USA, the UK and many other European countries
Number of participants	18,766 women (25% aged below 45 years, 36% aged 45–54 years, 34% aged 55–69 years and 6% aged 70 years or over; 33% premenopausal, 4% perimenopausal and 63% postmenopausal)
Population	Women with early breast cancer (not defined)
Inclusion criteria	No additional inclusion criteria were reported
Exclusion criteria	No exclusion criteria were reported
Intervention(s)	Adjuvant bisphosphonate treatment (mainly zoledronic acid 50%, clodronate 27% and ibandronic acid 16%)
Comparator(s)	Control group with no bisphosphonate treatment (open label or placebo)
Length of follow-up	Median follow-up was 5.6 woman-years (IQR 3.7 to 8.0 years). Mean scheduled treatment duration was 3.4 years and 97% of participants were in trials of 2–5 years' treatment

Outcomes	Primary outcomes: • any recurrence of breast cancer (distant, locoregional or new primary in the contralateral breast) • distant recurrence (ignoring any previous locoregional or contralateral recurrence) and • breast cancer mortality
	Secondary outcomes:[a] • all-cause mortality • death without recurrence • bone recurrence as the first distant recurrence (with or without concurrent other recurrence) • other first (extraskeletal) distant recurrence (with all analyses of distant recurrence ignoring any previous locoregional or contralateral recurrence) • locoregional recurrence as first event (ipsilateral breast, chest wall, or locoregional lymph nodes) • contralateral new primary breast cancer as first event, and • any bone fractures Prespecified primary subgroup investigations included site of first distant recurrence (bone or other site), menopausal status (or, if menopausal status was unavailable, years of age [less than 45 years, 54–54 years, 55 years or more]), and class of bisphosphonate (clodronate or aminobisphosphonate)
	Safety outcomes:[b] • Non-fatal adverse events such as ischaemic heart disease, stroke and osteonecrosis of the jaw
Source of funding	Funding for individual trials was chiefly from manufacturers. Funding for this analysis was from Cancer Research UK and the UK Medical Research Council. Clinical Trial Service Unit staff policy excludes honoraria or consultancy fees for any member of the EBCTCG

Overall risk of bias/quality assessment (CASP systematic review checklist and checklist for IPD meta-analyses[c])	Did the review address a clearly focused question?	Yes
	Did the authors look for the right type of papers?	Yes
	Do you think all the important, relevant studies were included?	Yes[d]
	Did the review's authors do enough to assess the quality of the included studies?	Unclear[e]
	If the results of the review have been combined, was it reasonable to do so?	Yes
	What are the overall results of the review?	See table 6
	How precise are the results?	See table 6
	Can the results be applied to the local population?	Yes
	Were all important outcomes considered?	Yes[f]
	Are the benefits worth the harms and costs?	See key points
Study limitations	• Information on how trials were identified, assessment of trial quality, and citations for excluded and included papers were not reported • Little or no information is available for some commonly used bisphosphonates, such as risedronate and alendronic acid • Limited information is available comparing different bisphosphonates, or different dosages of bisphosphonates • No information is available on managing breast cancer in men • Safety and quality of life outcome data are not reported • Combining the data for all bisphosphonates in the meta-analysis was controversial, as was including small trials not designed to measure the outcomes of interest and performing a meta-analysis of subgroups (CCO/ASCO and Jacobs C et al. 2015)	

Comments	[a] Results for many of these outcomes are not reported in this evidence summary. See the published paper for more details [b] Although data were collected, results for safety outcomes are not reported in the paper [c] Checklist for IPD meta-analyses of RCTs from Tierney et al. 2015 [d] A systematic review appears to have been undertaken but the methods of identifying trials, seeking collaboration, data collection, collation, checking, and presentation have not been fully reported, apart from to note these were undertaken as in previous EBCTCG reports. A protocol of the methods for this particular study is not reported. Individual participant data were not obtained for 6 of the 32 completed RCTs that recorded recurrence data, but these included only 525 women and would have been unlikely to change the outcomes of the meta-analysis [e] No assessment of quality or risk of bias of the individual trials is reported, including randomisation, allocation concealment, blinding and adjudication of outcomes. It is unclear whether or not the integrity of the IPD meta-analysis was checked [f] Outcomes and analyses were prespecified, although detailed methods of analyses were not reported (for example, methods for checking heterogeneity, and whether 1- or 2-stage IPD meta-analyses were performed). Safety outcomes were not reported for the study population; however, the adverse effect profile of bisphosphonates is well-established
Abbreviations: EBCTCG, Early Breast Cancer Trialists' Collaborative Group; IQR, interquartile range; IPD, individual participant meta-analysis; RCT, randomised controlled trial	

Results tables

Table 6 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2015)

	Bisphosphonates	Control	Analysis
Total n=18,766	n=9,856	n=8,910	
Primary outcomes			

Rate of recurrence of breast cancer	16.3% at 5 years 24.9% at 10 years	17.4% at 5 years 25.9% at 10 years	Difference at 10 years 1.1% (95% CI −0.7% to 2.9%), NSS Rate ratio 0.94 (95% CI 0.87 to 1.01) p=0.08, NSS
Rate of distant recurrence	13.5% at 5 years 20.4% at 10 years	14.8% at 5 years 21.8% at 10 years	Difference at 10 years 1.4% (95% CI −0.3% to 3.1%), NSS Rate ratio 0.92 (95% CI 0.85 to 0.99) p=0.03
Rate of breast cancer mortality	8.9% at 5 years 16.6% at 10 years	9.7% at 5 years 18.4% at 10 years	Difference at 10 years 1.7% (95% CI 0.0% to 3.5%) Rate ratio 0.91 (95% CI 0.83 to 0.99) p=0.04
Selected secondary outcome			
Bone recurrence	4.7% at 5 years 7.8% at 10 years	5.9% at 5 years 9.0% at 10 years	Difference at 10 years 1.1% (95% CI −0.1% to 2.3%), NSS Rate ratio 0.83 (95% CI 0.73 to 0.94) p=0.004
All-cause mortality	10.6% at 5 years 20.8% at 10 years	11.4% at 5 years 22.3% at 10 years	Difference at 10 years 1.6% (95% CI −0.36 to 3.56), NSS Rate ratio 0.92, 95% CI 0.85 to 1.00, p=0.06
Prespecified subgroup analyses in postmenopausal women			
Total n=11,767	**n=6,099**	**n=5,668**	
Rate of recurrence of breast cancer	13.4% at 5 years 22.8% at 10 years	15.8% at 5 years 25.8% at 10 years	Difference at 10 years 3.0% (95% CI 0.5% to 5.5%) Rate ratio 0.86 (95% CI 0.78 to 0.94) p=0.002
Rate of distant recurrence	11.1% at 5 years 17.9% at 10 years	13.6% at 5 years 21.2% at 10 years	Difference at 10 years 3.4% (95% CI 1.0% to 5.8%) Rate ratio 0.82 (95% CI 0.74 to 0.91) p=0.0003

Rate of breast cancer mortality	7.5% at 5 years 14.7% at 10 years	8.7% at 5 years 18.0% at 10 years	Difference at 10 years 3.3% (95% CI 0.8% to 5.7%) Rate ratio 0.82 (95% CI 0.73 to 0.93) p=0.002
Bone recurrence	3.6% at 5 years 6.6% at 10 years	5.4% at 5 years 8.8% at 10 years	Difference at 10 years 2.2% (95% CI 0.6% to 3.8%) Rate ratio 0.72 (95% CI 0.60 to 0.86) p=0.0002
All-cause mortality	9.5% at 5 years 21.1% at 10 years	10.8% at 5 years 23.5% at 10 years	Difference at 10 years 2.3% (95% CI −0.64 to 5.24), NSS Rate ratio 0.86, 95% CI 0.77 to 0.96, p=0.005
Safety and tolerability outcomes			
Although data on safety outcomes was collected, results are not reported in the paper. From the data obtained, it was not possible to assess the incidence of osteonecrosis of the jaw			
Abbreviations: CI, confidence interval; NSS, not statistically significant; p, p value			

Excluded studies

Study reference	Reason for exclusion
Charehbili A, van de Ven S, Smit VT et al. (2014) Addition of zoledronic acid to neoadjuvant chemotherapy does not enhance tumor response in patients with HER2-negative stage II/III breast cancer: the NEOZOTAC trial (BOOG 2010-01). Annals of oncology: official journal of the European Society for Medical Oncology 25(5), 998–1004	Does not report recurrence or survival
Fasching PA, Jud SM, Hauschild M et al. (2014) FemZone trial: a randomized phase II trial comparing neoadjuvant letrozole and zoledronic acid with letrozole in primary breast cancer patients. BMC Cancer 14, 66	Does not report recurrence or survival, and was terminated early

Gralow J, Barlow WE, Paterson AHG et al. (2014) SWOG S0307 phase III trial of bisphosphonates as adjuvant therapy in primary breast cancer: comparison of toxicities and patient-stated preference for oral versus intravenous delivery. Journal of clinical oncology 32(15 suppl. 1)	Conference abstract only
Hasegawa Y, Tanino H, Horiguchi J et al. (2015) Randomized controlled trial of zoledronic acid plus chemotherapy versus chemotherapy alone as neoadjuvant treatment of HER2-negative primary breast cancer (JONIE Study). PLoS ONE 10(12), e0143643	Does not report recurrence or survival
Wong MHF, Stockler MR and Pavlakis N. Bisphosphonates and other bone agents for breast cancer. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003474. DOI: 10.1002/14651858.CD003474.pub3	Meta-analysis superseded by the 2015 EBCTCG meta-analysis of individual patient data

Search strategy

Database: Medline

Platform: Ovid

Version: 1946 to March wk 5 2017

Search date: 07/04/2017

Number of results retrieved: 88

Search strategy:

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1 exp Breast Neoplasms/ (257990)

2 ((breast* or mammary) adj4 (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or malignan*)).tw. (265230)

3 1 or 2 (321579)

4 exp Diphosphonates/ (23662)

5 (bisphosphonate* or diphosphonate*).tw. (15702)

6 (alenato or alend or alendronate or alendros or alovell or arendal or bifemelan or bifosa or binosto or bonapex or defixal or dronal or endronax or eucalen or fixopan or fosalan or fosamax or fosmin or fosval or marvil or maxibone or neobon or oncalst or onclast or osdron or osdronat or oseotenk or osficar or oslene or osteofar or osteofos or osteopor or osteosan or osteovan or osticalcin or porosal or teiroc or tibolene or voroste or alendronic or fosavance).tw. (3653)

7 (bondenza or bondronat or bondronate or boniva or bonviva or destara or iasibon or ibandronate or ibandronic acid or quodixor).tw. (861)

8 (amidronate or aminohydroxypropanediphosphonic acid or aminohydroxypropyldiphosphonate or aminohydroxypropylidene or aminohydroxypropylidene diphosphonate or aminohydroxypropylidenebisphonic acid or aminohydroxypropylidenebisphosphonate or aminohydroxypropylidenediphosphonate or aminomux or apd or aredia or aredronet or ostepam or pamidrin or pamidro cell or pamidro-cell or pamidrocell or pamidromyl or pamidronat or pamidronate or pamifos or paminject or pamipro or pamired or pamisol or pamitor or panolin or panorin or ribodronat or texpami or pamidronic).tw. (6132)

9 (risedronate or actonel or atelvia or risedronic acid or benet or optinate or ribastamin or risedronic).tw. (1469)

10 (clodronic or dichloromethanediphosphonic or bonefos or clodronate or dichloromethanediphosphonate or dichloromethanediphosphonic acid or dichloromethylenebisphosphonate or difosfonal or lodronat or lodronate or mebonat or ossiten or ostac or clasteon or loron).tw. (1658)

11 (aclasta or orazol or reclast or zoledronate or zoledronic acid or zomera or zometa or zerlinda).tw. (3236)

12 or/4-11 (32684)

13 3 and 12 (2666)

14 randomized controlled trial.pt. (458924)

15 randomized controlled trial/ (458924)

16 controlled clinical trial.pt. (93874)

17 random allocation/ (91968)

18 Placebos/ (34857)

19 clinical trial, phase ii/ or clinical trial, phase iii/ (42481)

20 14 or 15 or 16 or 17 or 18 or 19 (650823)

21 animals/ (6075139)

22 humans/ (16769359)

23 21 not 22 (4347891)

24 20 not 23 (593032)

25 13 and 24 (310)

26 limit 25 to english language (298)

27 (2011* or 2012* or 2013* or 2014* or "2015 *" or 2016* or 2017*).ed. (4299379)

28 26 and 27 (88)

Database: Medline in-process

Platform: Ovid

Version: April 06 2017

Search date:07/04/2017

Number of results retrieved: 33

Search strategy:

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1 exp Breast Neoplasms/ (49)

2 ((breast* or mammary) adj4 (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or malignan*)).tw. (26121)

3 1 or 2 (26137)

4 exp Diphosphonates/ (1)

5 (bisphosphonate* or diphosphonate*).tw. (1931)

6 (alenato or alend or alendronate or alendros or alovell or arendal or bifemelan or bifosa or binosto or bonapex or defixal or dronal or endronax or eucalen or fixopan or fosalan or fosamax or fosmin or fosval or marvil or maxibone or neobon or oncalst or onclast or osdron or osdronat or oseotenk or osficar or oslene or osteofar or osteofos or osteopor or osteosan or osteovan or osticalcin or porosal or teiroc or tibolene or voroste or alendronic or fosavance).tw. (430)

7 (bondenza or bondronat or bondronate or boniva or bonviva or destara or iasibon or ibandronate or ibandronic acid or quodixor).tw. (107)

8 (amidronate or aminohydroxypropanediphosphonic acid or aminohydroxypropyldiphosphonate or aminohydroxypropylidene or aminohydroxypropylidene diphosphonate or aminohydroxypropylidenebisphonic acid or aminohydroxypropylidenebisphosphonate or aminohydroxypropylidenediphosphonate or aminomux or apd or aredia or aredronet or ostepam or pamidrin or pamidro cell or pamidro-cell or pamidrocell or pamidromyl or pamidronat or pamidronate or pamifos or paminject or pamipro or pamired or pamisol or pamitor or panolin or panorin or ribodronat or texpami or pamidronic).tw. (516)

9 (risedronate or actonel or atelvia or risedronic acid or benet or optinate or ribastamin or risedronic).tw. (153)

10 (clodronic or dichloromethanediphosphonic or bonefos or clodronate or dichloromethanediphosphonate or dichloromethanediphosphonic acid or

dichloromethylenebisphosphonate or difosfonal or lodronat or lodronate or mebonat or ossiten or ostac or clasteon or loron).tw. (142)

11 (aclasta or orazol or reclast or zoledronate or zoledronic acid or zomera or zometa or zerlinda).tw. (587)

12 or/4-11 (2965)

13 3 and 12 (287)

14 (random* or placebo* or control* or blind*).tw. (388933)

15 13 and 14 (72)

16 limit 15 to english language (72)

17 (2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).ed. (1178222)

18 16 and 17 (33)

Database: Medline epubs ahead of print

Platform: Ovid

Version: April 06 2017

Search date:07/04/2017

Number of results retrieved: 11

Search Strategy:

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1 exp Breast Neoplasms/ (0)

2 ((breast* or mammary) adj4 (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or malignan*)).tw. (6061)

3 1 or 2 (6061)

4 exp Diphosphonates/ (0)

5 (bisphosphonate* or diphosphonate*).tw. (245)

6 (alenato or alend or alendronate or alendros or alovell or arendal or bifemelan or bifosa or binosto or bonapex or defixal or dronal or endronax or eucalen or fixopan or fosalan or fosamax or fosmin or fosval or marvil or maxibone or neobon or oncalst or onclast or osdron or osdronat or oseotenk or osficar or oslene or osteofar or osteofos or osteopor or osteosan or osteovan or osticalcin or porosal or teiroc or tibolene or voroste or alendronic or fosavance).tw. (59)

7 (bondenza or bondronat or bondronate or boniva or bonviva or destara or iasibon or ibandronate or ibandronic acid or quodixor).tw. (6)

8 (amidronate or aminohydroxypropanediphosphonic acid or aminohydroxypropyldiphosphonate or aminohydroxypropylidene or aminohydroxypropylidene diphosphonate or aminohydroxypropylidenebisphonic acid or aminohydroxypropylidenebisphosphonate or aminohydroxypropylidenediphosphonate or aminomux or apd or aredia or aredronet or ostepam or pamidrin or pamidro cell or pamidro-cell or pamidrocell or pamidromyl or pamidronat or pamidronate or pamifos or paminject or pamipro or pamired or pamisol or pamitor or panolin or panorin or ribodronat or texpami or pamidronic).tw. (90)

9 (risedronate or actonel or atelvia or risedronic acid or benet or optinate or ribastamin or risedronic).tw. (13)

10 (clodronic or dichloromethanediphosphonic or bonefos or clodronate or dichloromethanediphosphonate or dichloromethanediphosphonic acid or dichloromethylenebisphosphonate or difosfonal or lodronat or lodronate or mebonat or ossiten or ostac or clasteon or loron).tw. (26)

11 (aclasta or orazol or reclast or zoledronate or zoledronic acid or zomera or zometa or zerlinda).tw. (83)

12 or/4-11 (423)

13 3 and 12 (44)

14 (random* or placebo* or control* or blind*).tw. (71361)

15 13 and 14 (11)

16 limit 15 to english language (11)

Database: Embase

Platform: Ovid

Version: 1974 to 2017 Week 14

Search date: 07/04/2017

Number of results retrieved: 393

Search strategy:

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1 exp *breast cancer/ (264740)

2 ((breast* or mammary) adj4 (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or malignan*)).tw. (394731)

3 1 or 2 (423305)

4 exp *bisphosphonic acid derivative/ (24597)

5 (bisphosphonate* or diphosphonate*).tw. (24959)

6 (alenato or alend or alendronate or alendros or alovell or arendal or bifemelan or bifosa or binosto or bonapex or defixal or dronal or endronax or eucalen or fixopan or fosalan or fosamax or fosmin or fosval or marvil or maxibone or neobon or oncalst or onclast or osdron or osdronat or oseotenk or osficar or oslene or osteofar or osteofos or osteopor or osteosan or osteovan or osticalcin or porosal or teiroc or tibolene or voroste or alendronic or fosavance).tw. (7300)

7 (bondenza or bondronat or bondronate or boniva or bonviva or destara or iasibon or ibandronate or ibandronic acid or quodixor).tw. (2143)

8 (amidronate or aminohydroxypropanediphosphonic acid or aminohydroxypropyldiphosphonate or aminohydroxypropylidene or aminohydroxypropylidene diphosphonate or aminohydroxypropylidenebisphonic acid or aminohydroxypropylidenebisphosphonate or aminohydroxypropylidenediphosphonate or aminomux or apd or aredia or aredronet or ostepam or pamidrin or pamidro cell or pamidro-cell or pamidrocell or pamidromyl or pamidronat or pamidronate or pamifos or paminject or pamipro or pamired or pamisol or pamitor or panolin or panorin or ribodronat or texpami or pamidronic).tw. (9689)

9 (risedronate or actonel or atelvia or risedronic acid or benet or optinate or ribastamin or risedronic).tw. (3155)

10 (clodronic or dichloromethanediphosphonic or bonefos or clodronate or dichloromethanediphosphonate or dichloromethanediphosphonic acid or dichloromethylenebisphosphonate or difosfonal or lodronat or lodronate or mebonat or ossiten or ostac or clasteon or loron).tw. (2761)

11 (aclasta or orazol or reclast or zoledronate or zoledronic acid or zomera or zometa or zerlinda).tw. (7394)

12 or/4-11 (46725)

13 3 and 12 (4031)

14 exp Clinical Trials/ (283882)

15 Randomization/ (85535)

16 Placebo/ (335538)

17 Double Blind Procedure/ (142603)

18 Single Blind Procedure/ (30608)

19 Crossover Procedure/ (55966)

20 ((random* or control* or clinical*) adj3 (trial* or stud*)).tw. (1343860)

21 (random* adj3 allocat*).tw. (34967)

22 placebo*.tw. (255879)

23 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. (201355)

24 (crossover* or (cross adj over*)).tw. (88145)

25 or/14-24 (1809520)

26 nonhuman/ not human/ (3791464)

27 25 not 26 (1749048)

28 13 and 27 (1457)

29 limit 28 to english language (1377)

30 (201104* or 201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc. (9553388)

31 29 and 30 (694)

32 limit 31 to (conference abstract or conference paper or conference proceeding or "conference review") (301)

33 31 not 32 (393)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED

Platform: Wiley

Version:

CDSR – 4 of 12 April 2017

DARE – 2 of 4, April 2015 (legacy database)

CENTRAL – 3 of 12 March 2017

HTA – 4 of 4 October 2016

NHS EED – 2 of 4, April 2015 (legacy database)

Search date: 07/04/2017

Number of results retrieved: CDSR 2; DARE 10 CENTRAL 249 ; HTA 0 ; NHS EED 3.

Search strategy:

Search Name: Breast cancer and bisphosphonates

Date Run: 07/04/17 11:03:14.233

Description:

ID Search Hits

#1 MeSH descriptor: [Breast Neoplasms] explode all trees 10139

#2 (breast* or mammary) near/4 (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or malignan*):ti,ab,kw (Word variations have been searched) 23796

#3 #1 or #2 23796

#4 MeSH descriptor: [Diphosphonates] explode all trees 2157

#5 bisphosphonate* or diphosphonate*:ti,ab,kw (Word variations have been searched) 2120

#6 alenato or alend or alendronate or alendros or alovell or arendal or bifemelan or bifosa or binosto or bonapex or defixal or dronal or endronax or eucalen or fixopan or fosalan or fosamax or fosmin or fosval or marvil or maxibone or neobon or oncalst or onclast or osdron or osdronat or oseotenk or osficar or oslene or osteofar or osteofos or osteopor or osteosan or osteovan or

osticalcin or porosal or teiroc or tibolene or voroste or alendronic or fosavance:ti,ab,kw (Word variations have been searched) 1084

#7 bondenza or bondronat or bondronate or boniva or bonviva or destara or iasibon or ibandronate or ibandronic acid or quodixor:ti,ab,kw (Word variations have been searched) 326

#8 amidronate or aminohydroxypropanediphosphonic acid or aminohydroxypropyldiphosphonate or aminohydroxypropylidene or aminohydroxypropylidene diphosphonate or aminohydroxypropylidenebisphonic acid or aminohydroxypropylidenebisphosphonate or aminohydroxypropylidenediphosphonate or aminomux or apd or aredia or aredronet or ostepam or pamidrin or pamidro cell or pamidro-cell or pamidrocell or pamidromyl or pamidronat or pamidronate or pamifos or paminject or pamipro or pamired or pamisol or pamitor or panolin or panorin or ribodronat or texpami or pamidronic:ti,ab,kw (Word variations have been searched) 676

#9 risedronate or actonel or atelvia or risedronic acid or benet or optinate or ribastamin or risedronic:ti,ab,kw (Word variations have been searched) 454

#10 clodronic or dichloromethanediphosphonic or bonefos or clodronate or dichloromethanediphosphonate or dichloromethanediphosphonic acid or dichloromethylenebisphosphonate or difosfonal or lodronat or lodronate or mebonat or ossiten or ostac or clasteon or loron:ti,ab,kw (Word variations have been searched) 333

#11 aclasta or orazol or reclast or zoledronate or zoledronic acid or zomera or zometa or zerlinda:ti,ab,kw (Word variations have been searched) 979

#12 {or #4-#11} 4101

#13 #3 and #12 Publication Year from 2011 to 2017 264

Development of this evidence summary

The evidence summaries: process guide (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers

Professor Robert Coleman, Department of Oncology and Metabolism, University of Sheffield.

Dr John Graham, Consultant Oncologist & Trust Cancer Lead Clinician, Musgrove Park Hospital.

Professor Chris Holcombe, Oncoplastic Breast Surgeon, Royal Liverpool University Hospital.

Dr Karen McAdam, Consultant Medical Oncologist, Cambridge University Hospitals NHS Foundation Trust.

Declarations of interest

Robert Coleman has previously received medical education fees for an unrelated topic from Eisai and Astra Zeneca. His institution currently receives research funding from Amgen and Bayer and has previously received research funding from Novartis. He has published extensively on this topic (including practice guidelines, and advice to commissioners and the Breast Cancer Clinical Reference Group), and contributed to the repurposing of drugs debate through his role as a Board member for Breast Cancer Now.

John Graham is a Clinical Adviser for the National Guideline Alliance, Royal College of Obstetricians & Gynaecologists, and the Vice Chair for NICE Guideline Updates Committee B. He is the principal investigator for various ongoing clinical trials in prostate cancer and breast cancer, 3 of which are funded by Bayer Health Care and 8 of which are run via the National Cancer Research Network, which is not pharmaceutical industry funded. He has received travel expenses from The Conference Forum to attend the Immuno-Oncology 360 Conference.

Chris Holcombe has been paid to chair an Advisory Board for Genomic Health and lecture on behalf of Roche. He has also accepted hospitality to attend a conference provided by the makers of Braxon, an Acellular Dermal Matrix used in breast reconstruction.

Karen McAdam has received a speaker fee from Roche for a meeting on neoadjuvant chemotherapy/anti HER2 therapy for early breast cancer. She previously sat on an advisory board for Novartis and is now an advisory board member for the EISAI First Thoughts meetings.

About this evidence summary

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

This summary is not NICE guidance.

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