# Implementation of Adjuvant Bisphosphonates for Early Breast Cancer Patients

NHS Northern Cancer Alliance

## Executive Summary

Following publication of a meta-analysis on the use of adjuvant bisphosphonates in early breast cancer[1], the National Institute of Clinical Excellence (NICE) issued an Evidence Summary in 2017[2] recommending their use in preventing recurrence and improving survival early breast cancer. This should have been implemented and adopted as standard care in but has not been.

**Northern Cancer Alliance (NCA) recommends that all provider Trusts ensure they have implemented this NICE guidance and make adjuvant bisphoponates available without further delay.**

*Key points for provider Trusts and CCG commissioners*

- Bisphosphonates are not licensed for this indication and must be used 'off-label'. NICE can only issue Technology Appraisals on licensed indications.
- Bisphosphonates for breast cancer patients are funded by CCGs as part of breast cancer services. They are not funded by NHS England.
- The evidence shows that use of adjuvant bisphosphonates reduce the rate of breast cancer recurrence in the bone and improves breast cancer survival in postmenopausal women. There is an absolute risk reduction in breast cancer death of 3.3% for postmenopausal women with early (curable) breast cancer.
- For every 100 patients treated with adjuvant bisphosphonates, 3 deaths from breast cancer will be prevented per annum. In NCA this means 27 to 45 early breast cancer patients will not progress to metastatic disease and die.
- The recommended treatment schedule is a 15-minute infusion of zoledronic acid 4mg in 100ml, which should be given in secondary care as a day case attendance, either on oncology day unit, ambulatory care unit or equivalent.
- The NCA Chemotherapy group recommends 3 years of treatment (7 doses) to reduce side effects and capacity burden. NICE recommended that patients have treatment every 6 months for 3 to 5 years but could not distigusih between the tewo treatment durations.
- Clinical consensus is that patients should be started on adjuvant zolendronate within 6 months of the completion of hospital based treatment, ie. Surgery, Chemo (including Herceptin) and radiotherapy.
- Drug costs are negligible, £7.88 per year, per patient. The main costs of the intervention are the cost of administering IV therapy in secondary care. This activity can generate a tariff of £401 per patient.
- Treatment numbers are unknown but estimated to be between 30 and 60 patients per 100,000 population each year, with numbers increasing each year for 3 years until steady state is reached. This means 915 to 1525 patients initially per year in the NCA.
- There is concern around capacity, however the weekly impact on oncology day units is small; an average of only 1 to 3 patients per week initially, rising to 6 to 12 over three years (per day unit)

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## Background

In 2015 a meta-analysis was published in the Lancet[1] which examined the risks and benefits of adjuvant bisphosphonate treatment in breast cancer. The meta-analysis showed adjuvant bisphosphonates reduce the rate of breast cancer recurrence in the bone and improve breast cancer survival in postmenopausal women.

The main bisphosphonates examined were ibandronic acid, zoledronic acid and clodronate. These medicines are licensed for prevention of bone fractures in adults with advanced cancer, for osteoporosis and for hypercalcaemia of malignancy.

The use of bisphosphonates for preventing recurrence or improving survival in patients with early breast cancer is not licensed, so use for this indication is off-label. As these medicines are now all generic (patent expired) they are never likely to be licensed for this indication as new licences only usually occur whilst a medicine is patent protected; thus the manufacturer can recover the cost of investing in new licence. This does not present any concerns as most traditional cytotoxic medicines used to treat cancer are used off-label.

This means that for this indication these drugs were unable to be subject to a NICE Technology Appraisal which if positive would require them to be commissioned for use in the NHS. Instead NICE issued a clinical evidence summary in July 2017[2]

The majority of medicines used to treat cancer are commissioned by NHS England, via a pass through arrangement from local Trusts to the regional specialised commissioning team. Only cancer medicines indication(s) and drug regimen combinations that have been approved by NICE, the Cancer Drug Fund and those that were historically in 'baseline' funding may be used.

NHS England does not commission hormonal treatments used in cancer or bisphosphonates as these are considered longer term treatments and are funded by CCGs as part of standard activity tariff funding for breast cancer services.

The lack of a single commissioner and fact that the NICE guidance was not mandatory means local commissioning involvement was needed for this intervention and delay in implementation. This has led to postcode prescribing and variation in access across the UK. In the NCA only 4 out of 9 NHS Trusts have implemented.

## Evidence Base

The NICE review is comprehensive and highlights the key findings of the meta-analysis carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG)[1.] The meta-analysis reviewed 26 randomised controlled trials involving nearly 19,000 women with primary breast cancer, over 11,000 of whom were post-menopausal. It showed benefits in post-menopausal women, but no benefits were seen in pre-menopausal women. The benefits of bisphosphonates were similar irrespective of histological type of breast cancer and the use of other treatments such as chemotherapy

- Reduced risk of breast cancer spreading to the bones within 10 years by 28%; Absolute risk reduction of 2.2% (from 8.8% to 6.6%)
- Reduced risk of breast cancer spreading (to any site, including bone) within 10 years by 18%; Absolute risk reduction of 3.3% (from 21.2% to 17.9%).
- Reduced risk of death from breast cancer within 10 years by 18%; Absolute risk reduction of 3.3% (from 18.0% to 14.7%)

NICE noted the meta-analysis has limitations due to 'the methods being poorly reported' and noted 'there is insufficient evidence to determine precise subgroups of postmenopausal women who would benefit, with a suggestion that the benefits might be less in women with low-risk cancers.'

Both European[3] and North American (CCO/ASCO)[4] expert groups recommend that bisphosphonates are used for postmenopausal women at intermediate or high-risk of recurrence of cancer and clinicians should use of decision-making tools such as Adjuvant! Online.

**Safety**

Bisphosphonates are not without risk or side effects. There is concern when using bisphosphonates on risk of osteonecrosis of the jaw (incidence 0.7%). Other common adverse effects include gastrointestinal effects with oral agents (such as nausea, dyspepsia, mild oesophagitis and abdominal pain) and bone, joint or muscle pain.

**Drug Choice**

Based on the evidence from the meta-analysis, both the CCO/ASCO and European consensus guidelines recommends one of following two treatment regimens:

| Medicine | Usual dosage | Cost per unit, excluding VAT | Annual cost, excluding VAT |
|---|---|---|---|
| IV zolendronic acid 4 mg/ 100 ml | 6-monthly for 3 to 5 years | £3.94 | £7.88 |
| Oral sodium clodronate 800 mg | 1600 mg daily for 2 to 3 years | £136.67 | £1781.59 |

***Note*** there was less evidence to support the other bisphosphonates and treatment schedules

Using the costs provided by NICE there is clear a cost difference between the two, with zoledronic acid proving much cheaper.

In addition, zoledronic acid is likely to be much better tolerated, oral clodronate is not a pleasant therapy for patients to take, the tablets are large and difficult to swallow, and are much more likely to cause gastrointestinal adverse effects than IV zoledronic acid. The six-monthly hospital visits for administration of zoledronic acid may be a disadvantage for some patients.

**Duration of therapy**

The trials included in the meta-analysis have a range of treatment durations hence the varying length of treatment in the NICE recommendation. As there is no clear advantage in longer duration of therapy the shorted duration should be preferred as uses fewer NHS resources reducing side effect burden for patients.

New evidence was presented in late 2017 suggesting that longer duration of therapy is not needed. The phase iii SUCCESS A trial, presented at the 2017 San Antonio Breast Cancer Symposium evaluated 5 years versus 2 years of adjuvant zoledronic acid treatment in high-risk early breast cancer patients.

The trial found no benefit for the longer duration; disease-free survival was the same in each arm, approximately 90% at 40 months[5].

This trial has not yet been published so results should be treated with caution as longer follow up may be needed. However whilst it may be too early to consider only 2 years of treatment, the results support the position that there is no clear benefit for treatment longer than 3 years.

**Recommendation**

In the NCA zoledronic Acid 4mg IV every 6 months for 3 years (7 doses) is the recommended bisphosphonate for reduce the risk of breast cancer recurrence in post-menopausal patients with early breast cancer.

## Patient Numbers

There is a high level of uncertainty when estimating patient number. When new oncology interventions are introduced patient numbers are often much lower than expected (local cancer drug fund data on file). In this case there is uncertainty around the stratification (and hence numbers) of low risk patients who will not need the intervention and higher risk patients who will.

A figure of 3,200 potentially eligible patients per year was calculated for the Scottish population (5.4 Million) which has a similar demographic to North East and Cumbria[6].

Using this calculation gives a figure of 592 potential patients per million per annum or 59 per 100,000 per year for NCA area.

However, this is likely to be the absolute maximum and, after low risk patients are stratified out, a more realistic estimate would be between 30 to 50 patients per 100,000 per year for the NCA.

## Commissioning position

This is a low-cost NICE recommended therapy, which is commissioned in Scotland and many areas of UK that could save approximately 27 to 45 lives in the North East (see below), therefore should be implemented without delay.

It was only a technicality of drug licensing that has prevented it being a mandatory NICE technology appraisal.

The majority of medicines used to treat cancer are commissioned by NHS England, via a pass-through arrangement from local Trusts to the regional specialised commissioning team. NHS England does not commission bisphosphonates (or hormonal treatments) as these are considered longer term treatments and, consequently, they are funded by CCGs as part of funding breast cancer services.

The intervention (drug and delivery cost) must be funded by CCGs.

The current access to adjuvant bisphosphonates across the NCA is varied and inequitable; it is in use in some Trusts (Durham and Darlington, North Tees & Hartlepool and Sunderland) and not in others, this mirrors the situation across UK.

## Cost of the Intervention

There should be no barrier due the drug costs; zoledronic acid is only £7.88 per patient per year (plus some additional costs for vitamin D supplementation for some patients.) It has been approved for this indication by most Trust Drug and Therapeutic Committees /Prescribing Committees. (e.g. it was approved by North of Tyne APC in 2017)

A barrier to universal adoption has been concerns from secondary care oncology day units over the capacity to manage the extra activity to deliver treatment for the prevalent patient population over next three years.

In addition, CCGs may have concerns on funding the new activity due to unknown numbers. CCGs need to agree the increase in Tariff's with their provider Trust(s).

How this activity is coded can vary and each organisation should check with its own coding teams. For example, from Durham and Darlington suggest each day case visit to secondary for delivery of adjuvant zoledronic acid 15-minute infusion can be coded to Primary Diagnosis C50.9 (malignant neoplasm of breast, unspecified) and OPCS Procedure Code X29.2 (Continuous intravenous infusion of therapeutic substance). This will generate an HRG (Healthcare Resource Group) Tariff of **£401** (JA12L)[7]

Therefore, each zoledronic acid patient will cost approximately £810 per annum (2 x £401 activity plus £7.88 drug cost).

This compares with cost of sodium clodronate of £1781.59 per year.

**Recommendation**

As each provider Trust implements the NICE guideline they must discuss the extra annual activity that will be chargeable (via coding) with their CCG commissioners, agree what income the CCG will provide. As numbers will rise for three years providers and CCGs must ensure the activity associated with the intervention is monitored as part of on-going contractual discussions.

## Impact for NCA Trusts

In NCA the potential patient numbers and costs are as below:

| Provider Trust | Approx. population | Annual Patient Numbers Year 0ne | | Cost of Activity (£) | | Drug cost (£) | |
|---|---|---|---|---|---|---|---|
| | | 30 per 100,000 | 50 per 100,000 | 30 per 100,000 | 50 per 100,000 | 30 per 100,000 | 50 per 100,000 |
| North Cumbria | 320,000 | 96 | 160 | 76,992 | 128,320 | 756 | 1,261 |
| Newcastle | 260,000 | 78 | 130 | 62,556 | 104,260 | 615 | 1,024 |
| Northumbria | 499,000 | 150 | 250 | 120,059 | 200,099 | 1,180 | 1,966 |
| Queen Elizabeth Gateshead | 191,000 | 57 | 96 | 45,955 | 76,591 | 452 | 753 |
| South Tyneside | 153,000 | 46 | 77 | 36,812 | 61,353 | 362 | 603 |
| Sunderland | 343,000 | 103 | 172 | 82,526 | 137,543 | 811 | 1,351 |
| Durham and Darlington | 596,000 | 179 | 298 | 143,398 | 238,996 | 1,409 | 2,348 |
| James Cook Middlesbrough | 411,000 | 123 | 206 | 98,887 | 164,811 | 972 | 1,619 |
| North Tees and Hartlepool | 276,000 | 83 | 138 | 66,406 | 110,676 | 652 | 1,087 |

**Note -** as treatment is given for three years patient numbers will increase in year two and year three before reaching steady state.

## Savings

There is an incidental saving to CCGs on DEXA scans (which are not needed during treatment with adjuvant bisphosphonates) of £58 per scan per patient per year (HRG Tariff RD50Z)[7]. As a result, across the NCA Provider Trusts saving could be:

| Provider Trust | Approx. population | Annual Patient Numbers Year 0ne | | DEXA Scan Savings | |
|---|---|---|---|---|---|
| | | 30 per 100,000 | 50 per 100,000 | 30 per 100,000 | 50 per 100,000 |
| North Cumbria | 320,000 | 96 | 160 | 5,568 | 9,280 |
| Newcastle | 260,000 | 78 | 130 | 4,524 | 7,540 |
| Northumbria | 499,000 | 150 | 250 | 8,683 | 14,471 |
| Queen Elizabeth Gateshead | 191,000 | 57 | 96 | 3,323 | 5,539 |
| South Tyneside | 153,000 | 46 | 77 | 2,662 | 4,437 |
| Sunderland | 343,000 | 103 | 172 | 5,968 | 9,947 |
| Durham and Darlington | 596,000 | 179 | 298 | 10,370 | 17,284 |
| James Cook Middlesbrough | 411,000 | 123 | 206 | 7,151 | 11,919 |
| North Tees and Hartlepool | 276,000 | 83 | 138 | 4,802 | 8,004 |
| TOTAL | | 915 | 1,525 | | |

### *Reduction in deaths from breast cancer*

There is also a wider saving to the NHS based on number of lives saved, this is difficult to estimate but if the treatment works there is an absolute risk reduction in death of 3.3% and in risk metastatic disease in bones of 2.2%. This means there will be a 2 to 3% reduction in cases of metastatic breast cancer per annum. Given total numbers in NCA of between 915 to 1,525 patients to be treated this means up to 27 to 45 early deaths can be prevented. (0.03 x 915 and 0.03 x 1525 respectively).

The lifetime costs of treating metastatic breast cancer to the NHS are very hard to estimate and would be shared among provider Trusts, NHS England and CCG commissioners. Given the cost of drugs used and repeated number of admissions and clinic visits it would not be unreasonable to estimate an annual cost of at least £20,000 per patient (it is likely to be much higher).

A crude estimate for illustration purposes only is on basis of 2 to 3 % absolute risk reduction, is for every 100 patients treated the NHS would save £40,000 to £60,000.

**Using the estimate of 27 to 45, NCA savings could be £540,000 to £900,000.**

## Barriers to Implementation

The impact on oncology day unit capacity is widely perceived as a major barrier to implementation. It is true there will be a large number of additional treatments per annum but in reality the treatments are straightforward only requiring 30 minutes of nurse and chair time and no additional pharmacy time.

When viewed as weekly numbers as below, the impact on oncology day units is small and should be manageable given oncology day units have to constantly absorb additional NICE approvals e.g. immunotherapies.

| Provider Trust | Approx. population | Annual Patient Numbers | | Weekly Numbers Year One | | Weekly Numbers Year Two | | Weekly Numbers Year Three | |
|---|---|---|---|---|---|---|---|---|---|
| | | 30 per 100,000 | 50 per 100,000 | 30 per 100,000 | 50 per 100,000 | 30 per 100,000 | 50 per 100,000 | 30 per 100,000 | 50 per 100,000 |
| North Cumbria | 320,000 | 96 | 160 | 2 | 3 | 4 | 6 | 6 | 9 |
| Newcastle | 260,000 | 78 | 130 | 2 | 3 | 3 | 5 | 5 | 8 |
| Northumbria | 499,000 | 150 | 250 | 3 | 5 | 6 | 10 | 9 | 14 |
| QE Gateshead | 191,000 | 57 | 96 | 1 | 2 | 2 | 4 | 3 | 6 |
| South Tyneside | 153,000 | 46 | 77 | 1 | 1 | 2 | 3 | 3 | 4 |
| Sunderland | 343,000 | 103 | 172 | 2 | 3 | 4 | 7 | 6 | 10 |
| Durham and Darlington | 596,000 | 179 | 298 | 3 | 6 | 7 | 11 | 10 | 17 |
| James Cook Middlesbrough | 411,000 | 123 | 206 | 2 | 4 | 5 | 8 | 7 | 12 |
| North Tees & Hartlepool | 276,000 | 83 | 138 | 2 | 3 | 3 | 5 | 5 | 8 |

*Opportunities for Providers*

Provider Trusts could look at setting up a weekly clinic slot and schedule the bisphosphonates at same time, e.g. evening session. A minimum of one qualified chemotherapy nurse, plus another qualified member of staff to check drugs would be needed. Funding will depend on negotiations with local CCGs for activity tariff.

However lack of funding should not be a barrier to implementation for this NICE approved intervention.

## Conclusions

If the remaining Trusts in NCA who have not implemented do not start offering adjuvant bisphosphonates, then there will not be a reduction in breast cancer deaths.

The uncertainty on capacity impact of the intervention has been a barrier to implementation; however that driven by concerns over the higher numbers when 5 years of treatment was proposed.

By supporting the recommendations of this paper for 3 years treatment rather than 5 the capacity impact is manageable.

Given the very small numbers in year one, Trusts have time to implement in year and then negotiate with CCGs for increase in tariff activity for future years as numbers rise.

CCGs should be assured that the overall cost of this intervention will be offset by the reduction in costs associated with DEXA scans and the savings made by preventing metastatic breast cancers and potentially saving 3 lives per 100

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On behalf of Norther Cancer Alliance Chemotherapy Group, August 2018

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## References (click tom open relevant documents


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