Appendix A

Study summaries have been ordered as they appear in the exceptional surveillance review evidence summary:

A Cochrane review (O'Carrigan et al. 2017) searched for randomised control trial (RCT) evidence published up to 19th September 2016 which included evidence on the effectiveness of adjuvant bisphosphonates in women with early breast cancer. A meta-analysis of data from 9 RCTs (n=13,949 with a follow-up period ranging from 3 to 10 years; rated as high-quality evidence using GRADE) found that bisphosphonates were associated with a significant overall survival benefit compared with placebo and/or no bisphosphonate (studies mainly included intravenous (IV) zoledronate 4 mg every 3 weeks (4 RCTs) or clodronate 1600 mg/day (4 RCTs); ibandronate 50 mg/day, or pamidronate 300 mg/day were also included). A sub-group analysis found that there was a significant survival benefit from bisphosphonates (specifically zoledronate or clodronate) in postmenopausal women, but not for premenopausal women. For disease-free survival the only significant benefit from bisphosphonates was found for postmenopausal women with early breast cancer (sub-group analysis of 7 RCTs, n=8,314 women; high-quality evidence). Thirty-five cases of osteonecrosis of the jaw were identified out of 7,047 women who received bisphosphonates (9 RCTs, n=13,242; high-quality evidence), with most of these events occurring in patients in 2 of the 6 RCTs that used zoledronate. Compared with placebo or no bisphosphonates, bisphosphonates did not significantly reduce the incidence of fractures in women with early breast cancer.

A systematic review (Liu et al. 2021) assessing the effectiveness of adjuvant bisphosphonates on overall survival in breast cancer patients with no evidence of any relapse or metastasis found that, based on a meta-analysis of data from 17 RCTs (n=14,609), bisphosphonate use resulted in a significant benefit on overall survival for up to more than 4 years after treatment completion in breast cancer patients compared with a placebo or no-placebo control.

An RCT (De Groot et al. 2019) assessed the effectiveness of chemotherapy with or without 4 mg IV zoledronic acid administered within 24 h of chemotherapy repeated every 3 weeks for 6 cycles in 246 women with HER2-negative, stage II or III breast

cancer. Median follow-up was 6.4 years. There was no difference in disease-free survival between the treatment groups, but overall survival was found to be significantly worse in patients who received zoledronic acid. In a sub-group analysis based on menopausal status, no significant differences were found in disease-free survival or overall survival in postmenopausal patients between the treatment groups, nor in premenopausal patients.

An RCT (Coleman et al. 2017) reported on a sub-group analysis of data from the AZURE trial: an open-label phase 3 RCT assessing the effectiveness of standard adjuvant systemic therapy plus IV zoledronic acid every 3-4 weeks for 6 doses, then every 3-6 months until the end of 5 years compared with adjuvant systemic therapy alone in patients with stage II or III breast cancer. Out of 1,739 Primary tumour samples, 420 in the zoledronic acid group and 445 in the control group could be assessed for MAF amplification (a biomarker for bone metastasis): 99 were MAF-positive in the zoledronic acid group and 85 in the control group. The study assessed invasive-disease-free survival (excludes in situ cancer events), rather than disease-free-survival, but did find that in patients with MAF-negative tumours, zoledronic acid was associated with significantly higher invasive-disease-free survival than those in the control group; whereas there was no difference between the treatment and control groups in invasive-disease-free survival for patients who had MAF-positive tumours. However, in patients 'not postmenopausal' with MAF-positive tumours (n=121), zoledronic acid was associated significantly lower invasive-disease-free survival and overall survival when compared with the control group.

A retrospective analysis of data from an RCT assessing the effectiveness of adjuvant systemic treatment plus 3 years oral clodronate (1600 mg daily) compared with placebo in 3,311 patients with early stage breast cancer (Paterson et al. 2021) was undertaken to validate the findings from Coleman et al.'s 2017 findings on MAF amplification and the effects of adjuvant zoledronic acid. MAF status could be assessed in 1,883 primary tumour samples (n=936 clodronate, n= 947 placebo). At 5 years follow-up, there was a significant benefit of clodronate compared with placebo in patients with MAF-negative tumours for both disease-free survival and overall survival; whereas in patients with MAF-positive tumours, the authors reported that

there was no benefit of clodronate ‘but rather possible harm in some subgroups’ and no association was found between MAF status and menopausal status.

A phase 3 open-label RCT (Vliek et al. 2022) assessed disease-free survival in postmenopausal women with oestrogen receptor-positive stage I to III breast cancer with an indication for adjuvant endocrine therapy randomised to receive either adjuvant oral ibandronate 50 mg once daily for 3 years (n=566) or no adjuvant treatment (n=551). There was no significant different in disease-free survival between the groups at follow-up (median follow-up was 8.5 years). Compared with the control group, patients on ibandronate experienced significantly more gastrointestinal issues and 11 of 566 (1.9%) developed osteonecrosis of the jaw.

A systematic review and meta-analysis (Yang et al. 2019) of 23 RCTs providing data on adverse events from bisphosphonate therapy compared with no bisphosphonates in breast cancer patients found that flu-like illness, fatigue, fever, dyspepsia, anorexia and urinary tract infection were significantly associated with bisphosphonate use. Meta-analysis of data on osteonecrosis of the jaw was from observational studies only and so does not meet inclusion criteria.

A systematic review and network meta-analysis (Jackson et al. 2021) of 56 RCTs providing data on adverse events from bisphosphonate therapy (zoledronic acid, ibandronate, pamidronate, alendronate or clodronate) in breast cancer patients (total n=29,248; n=18,301 receiving bisphosphonates) and an examination of individual-level patient data from the AZURE RCT reported that there were 24 adverse outcomes that were significantly increased in patients receiving bisphosphonates. The authors note that most of these are known side-effect such as fever, headache increased bone pain, cardiac events, hypocalcaemia and osteonecrosis of the jaw (84 cases out of 18,301 taking bisphosphonates); but they also identified 4 previously unrecognised adverse effects: fatigue, neurosensory problems, hypertonia/muscle spasms and possibly dysgeusia. They also reported that ‘several symptoms previously reported as potential side effects in the literature were not significantly increased in this analysis: constipation, insomnia, respiratory problems, oedema or thirst/dry mouth’; and the individual patient-level data and sub-group analysis ‘revealed little variation in side effects between women of different ages or

menopausal status, those with metastatic versus non-metastatic cancer, or between women receiving different concurrent breast cancer therapies'

An RCT (Kizub et al. 2021) reported on the risk factors for osteonecrosis of the jaw based on findings from the S0307 RCT (Gralow et al. 2020). The S0307 RCT implemented guidelines for the prevention of osteonecrosis of the jaw and collected information about dental health and development of osteonecrosis of the jaw. Within the RCT, at 3 years follow-up 48 of 6,018 women developed osteonecrosis of the jaw. There was a significant difference in time to developing osteonecrosis of the jaw between the different bisphosphonates, with time to development of osteonecrosis of the jaw being similar between those receiving zoledronic acid or ibandronate, but longer for those taking clodronate (median time was 2.1 years, 2.0 years and 3.4 years respectively). People taking zoledronic acid were significantly more likely to develop osteonecrosis of the jaw compared with the other 2 bisphosphonates and worse dental health (measured by dental calculus, gingivitis, moderate or severe periodontal disease and periodontitis > 4 mm) was associated with a significant increase in the odds of developing osteonecrosis of the jaw.

A network meta-analysis (Miyashita et al. 2020) compared the efficacy of zoledronate, risedronate (and denosumab: a bone modifying agent not included in this evidence review) in patients with breast cancer receiving adjuvant aromatase inhibitors on the risk of fracture reported in 16 RCTs (n=not reported in abstract). It found that risedronate (but not zoledronate) was associated with a significantly lower risk of fracture compared with the patients 'without upfront treatment'; that risedronate was associated with a significant increase in lumbar spine and total hip bone mineral density at 1 and 2 years compared with no treatment, but the bone mineral density results for people on adjuvant zoledronic acid were significantly better than for those on risedronate.

An RCT (Wilson et al. 2018) reported on results from the AZURE trial on the impact of adjuvant zoledronic acid on the 5-year fracture rate in women with stage II or III breast cancer (n=not reported in abstract). They found that compared with no bisphosphonate, zoledronic acid was associated with a significant increase in time-to-first fracture, that most fracture prevention benefit occurred however after a

disease-free survival event, and findings were similar between premenopausal and postmenopausal women.

A systematic review with meta-analysis (Bassatne et al. 2022) of 14 RCTs (n=not reported in abstract) reported on the effect of adjuvant zoledronic acid (7 RCTs) and oral bisphosphonates (6 RCTs) (and denosumab: 1 RCT) on bone mineral density in postmenopausal patients with non-metastatic breast cancer on aromatase inhibitors. It found that zoledronic acid and oral bisphosphonates compared with a control were associated with significant positive differences in bone mineral density at the lumbar spine and the total hip at 12months follow-up.

A systematic review with meta-analysis (Mei et al. 2020) of 13 RCTs (n=7,375) reported on the effect of adjuvant zoledronic acid compared with control on bone mineral density in patients with early breast cancer at 12 months follow-up. They found that zoledronic acid was associated with a significant increase in lumbar spine, total hip and femoral neck bone mineral density for the whole population; a significant increase in lumbar spine bone mineral density in premenopausal patients; and a significant increase in lumbar spine and total hip bone mineral density in postmenopausal patients.

An RCT (Kyvernitakis et al. 2018) assessed bone loss in patients with early breast cancer on 2-years of adjuvant treatment with 4 mg IV zoledronic acid every 3 months (n=34) compared with placebo (n=34). At 24 months follow-up there was a significant difference in lumbar spine bone mass density, with patients on zoledronic acid showing an increase in bone mass density, while controls showed a decrease. At 5 years follow-up both groups showed a decrease in bone mass density at the lumbar spine, but this was significantly less in the zoledronic acid group. For total hip and femoral neck bone mass density patients in the placebo group showed a significant decrease while those on zoledronic acid were at baseline bone mass density.