Efficacy of Pamidronate infusions for treatment of Complex Regional Pain Syndrome (CRPS)

IPM Item: IN60

Evidence-based Review

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Date:	March 2016
Status:	Final

Important note

- *The purpose of this report is to outline and interpret the best current evidence for the efficacy of pamidronate infusions in the treatment of Complex Regional Pain Syndrome Type 1 (CRPS-1) for pain.*
- *It is not intended to replace clinical judgement or be used as a clinical protocol.*
- *A reasonable attempt has been made to find and review papers relevant to the focus of this report; however, it does not claim to be exhaustive.*
- *This document has been prepared by the staff of the Evidence Based Healthcare Team, ACC Research. The content does not necessarily represent the official view of ACC or represent ACC policy.*
- *This report is based upon information supplied up to October 2015.*

Revision History

Date	Version	Description	Author
December 2015	V1.1	AB peer-review and proof read	Melissa Barry
December 2015	V1.2	External Peer-reviewer (TC) comments added	Melissa Barry
March 2016	Final	Presented to Purchasing Guidance Advisory Group	Melissa Barry

Executive Summary

Background

Pamidronate Disodium (Pamidronate, brand name: Aredia) is a bisphosphonate that can be administered intravenously as an infusion and is available in New Zealand. It is used to prevent the loss of bone mass by preventing bone resorption, and has been used in the treatment of Complex Regional Pain Syndrome (CRPS) to manage pain. The underlying physiological mechanism of how it does this is unknown. ACC has funded its use for claims in the past; however the current Interventional Pain Management (IPM) guidance does not provide a recommendation for its purchase.

The purpose of this evidence-based report is to analyse the available evidence on the efficacy of pamidronate infusion for the treatment of pain related to CRPS. This will help inform and facilitate consistent decision making in the future for pamidronate infusions for treating pain from CRPS.

Methodology

A systematic search of multiple databases found there was a paucity of studies regarding the efficacy of pamidronate infusions for pain in CRPS. The search revealed one randomised control trial (RCT) and two case-series that met the inclusion criteria. Using SIGN criteria these were appraised to provide moderate (RCT) and low (case-series) levels of evidence.

Main results

Overall the RCT and case-series found that within variable cohorts pamidronate did reduce pain scores and help improve function in participants with CRPS-1. None of the studies reported people with CRPS-2. Although the case-series both used much higher doses of pamidronate (151 ± 39mg and 180mg), a reduction in pain scores and increase in quality of life scores (SF-36 and range of movement at the affected joint) were still seen in the RCT which used a much lower dose (60mg). Adverse effects of pamidronate (Table 6) were reported to largely resolve without any further intervention. In general pamidronate infusion appears to be effective in decreasing pain in people with CRPS-1 at a lower dose of 60mg.

There is a paucity of studies that have investigated pamidronate infusions in CRPS. Although the best evidence for this treatment comes from a single RCT, other guidelines have used this evidence to support their recommendations (see table 1).

Conclusions

There is a paucity of studies that provide moderate to low levels of evidence for the efficacy of pamidronate infusions for treatment of pain in people with CRPS. A limitation within the studies is the variability across the studies with regard to: patient cohorts; dose of pamidronate; how variables were measured and the length of time the effects were measured for after a single infusion. There was also variability within studies as participants were at different stages of CRPS, had CRPS in different anatomical sites (upper or lower limb), or CRPS from traumatic and non-traumatic events. This was reflected within the statistical variability reported in the studies; however a statistically significant reduction in pain and increase in function scores was still found. This indicates these findings could be relevant to a range of different types of claimants diagnosed with CRPS-1.

Recommendations

Due to the paucity of studies and variability within this small number of studies, it is difficult to make a definitive recommendation with regard to the use of pamidronate for the treatment of CRPS-1. However it should also be taken into account that guidelines recommending the use of pamidronate have derived their recommendations from the same evidence sources.

The recommendation from the evidence is purchase on a case-by-case basis.

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1 Background

1.1 Description of Pamidronate infusion and CRPS

1.1.1 Pamidronate infusion

Pamidronate Disodium (Pamidronate, brand name: Aredia) is a compound that is administered intravenously as an infusion. It is a bisphosphonate, which is a class of drugs that prevent the loss of bone mass by preventing bone resorption. Currently pamidronate along with zoledronate are the only members of the bisphosphonate family which are available to be administered as an infusion in New Zealand (Medsafe, retrieved October 2015). It has been used in the treatment of Complex Regional Pain Syndrome (CRPS) to manage pain; however the evidence from the peer-reviewed literature about its effectiveness is limited.

The underlying mechanism by which pamidronate reduces pain is unclear. It is a potent inhibitor of osteoclastic activity and does this by binding to hydroxyapatite crystals in the bone, thus stopping the osteoclast precursors from binding to bone and maturing to fully functioning bone-resorbing osteoclasts (http://www.medsafe.govt.nz/searchResults.asp?q=pamidronate). Pamidronate is indicated for bone remodelling disorders like Paget's disease and in clinical trials is shown to be effective in cancers where there is considerable bone destruction (eg osteolysis in breast cancer and myelomas). These patients may also have decreased bone pain with pamidronate (http://www.medsafe.govt.nz/searchResults.asp?q=pamidronate), possibly brought about by its inhibiting of pain receptors (antinociceptive effect).

Adverse events associated with pamidronate use range from mild (influenza type symptoms, or irritation around the infusion site) to high severity (osteonecrosis in the maxilla and mandible[1]). For bisphosphonates in general, adverse events may increase with: the dose given; the time period over which a patient receives recurring infusions; whether it is given with other types of therapies (chemotherapy, radiotherapy, corticosteroids); and presence of co-morbidities (eg anaemia, infection, pre-existing oral disease), (http://www.medsafe.govt.nz/searchResults.asp?q=pamidronaterefs).

1.1.2 Brief description of CRPS

Complex Regional Pain Syndrome (CRPS) is a complex and poorly understood pain syndrome that occurs after an injury. There are two types: Type 1 (formerly known as reflex sympathetic dystrophy or RSD) where symptoms develop after a minor trauma or fracture but there is no detectable nerve lesion; and Type 2 (formerly known as causalgia) where after injury symptoms occur and there is nerve injury. Symptoms include: different types of pain that include burning, sharp, shooting, squeezing or throbbing; hyperalgesia; impairment of motor function; sympathetic dysfunction leading to the limb turning blue and swelling; and excessive sweating[2, 3].

There are a number of treatments available for CRPS - physiotherapy, neuromodulation of central pain pathways and regional nerve blocks. Medications include corticosteroids, topical analgesics, opioids, anticonvulsants and antidepressants[2, 3]. Bisphosphonates have shown some effectiveness in alleviating pain in people with CRPS as well as other types of pain (eg lower back pain, see section 2.2 on page 8). In this report the research articles report results for CRPS 1 or RSD.

1.1.3 Treatment of CRPS with Pamidronate

The physiological mechanism by which bisphosphonates decrease pain in people with CRPS is unknown. Bisphosphonates inhibit osteoclast activity, so maintain bone density and may have a role in preventing microfractures associated with CRPS pain. As mentioned previously, it is also hypothesised that bisphosphonates may have a role in modulating inflammatory pain responses (nociceptor activity) [4].

Recommendations on the use of pamidronate for CRPS in guidelines from other organisations are variable, however they all appear to reference the same RCT by Robinson et al, 2004[4]. The guidelines regarding pamidronate infusions are summarised in the table below.

Table 1. Overview of guidelines or policies from other organisations that refer to pamidronate use in CRPS

Guideline	Guidance for pamidronate infusion	Evidence reported by the guideline
Harden et al, 2013 [5] ***CRPS: Practical Diagnostic and Treatment Guidelines, 4th edition.*** ***Pain Medicine*, *14*(2), 180-229.**	Pharmacotherapy guide (Table 9 in document) Guidance refers to bisphosphonates in general: *Reason for inability to begin or progress pain treatment:* Significant allodynia/hyperalgesia *Action:* Calcitonin or Bisphosphonates	*Pamidronate references:* Robinson et al, 2004 Kubalek et al, 2001
Mailis and Taenzer, 2012 [6] ***Evidence-based guideline for neuropathic pain interventional treatments: Spinal cord stimulation, intravenous infusions, epidural injections and nerve blocks*** ***Journal of the Canadian Pain Society, 17(3),* 150**	IV Bisphosphonates (pamidronate not mentioned by itself): For patients with CRPS, who have not responded adequately to less invasive options, clinicians may consider a trial of IV bisphosphonates, which may produce long term (>1 month) benefit. Evidence quality (as defined in article): Good; Certainty: Moderate; Strength of recommendation Grade B (Recommend. High certainty with moderate effect or moderate certainty with moderate to substantial effect.	Robinson et al, 2004
Royal College of Physicians ***Complex regional pain syndrome in adults: UK guidelines for diagnosis, referral and management in primary and secondary care (May 2012)*** **https://www.rcplondon.ac.uk/projects/concise-guidelines**	The following guidance for management of CRPS for pain physicians and neurosurgeons with a special interest in the management of pain are: - Pamidronate (60 mg intravenous dose) should be considered for suitable patients with CRPS less than 6 months in duration as a one-off treatment *Stated in footnote for this recommendation: "The panel recognises that there may be other, newer types of bisphosphonates that may be appropriate/available in equivalent doses"*	Stated evidence from a High-quality trial and that evidence regarding pamidronate and CRPS is from a summary of NICE guidelines (2010)[a] and IASP (International Association for the Treatment of Pain) recommendations for neuropathic pain.
Aetna Policy **Number: 0672** **http://www.aetna.com/cpb/medical/data/600_699/0672.html** **Last reviewed by Aetna: 23/10/2015** **Retrieved by ACC reviewer: 30 November 2015**	Aredia and pamidronate: Subject to precertification: Aetna considers these drugs to be medically necessary for those members who meet precertification criteria. A list of bone disorders are included in this policy for pamidronate including: - "Complex regional pain syndrome refractory to other treatments"	A list of references provided with policy, however none are referred to specifically for CRPS. Robinson et al (2004) not included.

[a] The RCP guideline references the NICE guidance CG96 which referenced Robinson et al, 2004 however this is not publicly available anymore. The new 2013 guideline (www.nice.org.uk/guidance/CG173) does not include a recommendation for pamidronate or Aredia

1.2 Bisphosphonates used to treat other pain syndromes

As a direct continuation of the original IPM 2005 guidance an initial search was conducted for studies on the efficacy of bisphosphonate infusions for treating pain. This search was initially restricted to RCTs published since 2004 that were not included within the original guidance. A total of five RCTs of moderate to high quality were found. However during the analysis of this research it was determined that the focus of most of these studies did not fit the purposes of ACC for one or more of the following reasons:

- They included bisphosphonates that are not available in New Zealand and so these findings were not applicable for ACC claims
- They included patient cohorts that are outside of the scope of ACC legislation (eg Osteoarthritis, modal changes)

From this reasoning four of the five RCTs [7-10] were excluded from the main body of this report; however the findings are included within Appendix 2 at the end of this report.

The main finding from these excluded studies was that there was a paucity of RCTs that have investigated the efficacy of using bisphosphonates to treat pain from different bone disorders. Overall the RCTs report that bisphosphonates appear to reduce pain. However, summarising the overall efficacy of bisphosphonates for use in pain disorders is difficult due to the variable nature of the studies. Variability included different bisphosphonates at different doses, different patient cohorts, and different ways of measuring outcomes. The variability makes it difficult to come to a succinct conclusion on the efficacy of bisphosphonates for pain syndromes and construct recommendations for their use. To be able to answer this research question further RCTs are required for each type of bisphosphonate infusion, and would need to be grouped into similar pain disorders.

1.3 ACC's current position

On the current ACC Interventional Pain Management (IPM) website (http://www.acc.co.nz/for-providers/clinical-best-practice/interventional-pain-management/interventions/intervention-index/index.htm) evidence is presented for two bisphosphonates (alendronate and clodronate) that are not available in New Zealand as an infusion. Within the current IPM guidance pamidronate is not included as an item.

It is stated by the ACC Pharmaceutical Advisor that pamidronate infusions (IPM item: IN60) are funded for claims for CRPS. One other bisphosphonate infusion (zoledronate) is used for other disorders, predominantly to prevent bone loss (*personal communication with Pharmaceutical Advisor).*

1.4 Objective of this report

Upon consultation with the ACC Pharmaceutical Advisor and the IPM working group separately it was decided that the primary purpose of this evidence-based report is to analyse the available evidence on the effectiveness of pamidronate infusion for treatment of pain related to CRPS. A secondary request was to provide a brief overview of the effectiveness of bisphosphonates for use in other pain modalities.

Taking this into consideration this report is presented in two parts:

I. Help inform and facilitate consistent decision making with regard to pamidronate infusions for the treatment of CRPS

II. Provide an overview of other bisphosphonate infusions available in New Zealand and the efficacy of their use for the treatment of different types of pain (in Appendix 2).

2 Methodology

2.1 Search Strategy

A systematic search was conducted over multiple databases using search terms as described below by two ACC research advisors.

Searches were conducted in March 2015 and September 2015 in the following databases:

- AMED (Allied and Complementary Medicine) <1985 to May 2014>
- Embase <1988 to 2014 May 16>
- Pre-MEDLINE
- Ovid MEDLINE <1946 to Present>,
- Google scholar
- Ovid Nursing Database

Search terms included: pamidronate, aredia or Pamimed, complex regional pain syndrome, reflex sympathetic dystrophy or causalgia or CRPS or RSD,

See Appendix 1a for the search strategy.

2.1.1 Inclusion and Exclusion Criteria

The original literature search conducted in March 2015 was limited to RCTs. As only one RCT was found it was decided in consultation with the IPM Working Group and the business owner to extend the search to include study designs of lower quality (eg case-series and case-control studies).

Inclusion Criteria

- Types of studies: Systematic reviews, randomised controlled studies, case-series, case controls
- Types of participant: Adults with CRPS
- Types of interventions: Pamidronate infusion
- Types of comparison: saline placebo
- Types of variable/comparisons: measures that assessed level of pain (eg visual analogue scale),

Exclusion Criteria

- Single case studies
- Grey literature (eg conference proceedings, non-peer-reviewed literature), literature reviews
- Animal or laboratory studies
- Non-English studies
- Other types of bisphosphonate infusion not used for CRPS, or not available in New Zealand (eg clodronate, zoledronate)
- Pamidronate infusions used for patient cohorts other than CRPS (eg different types of cancers, bone lesions or modal changes)

2.2 Level of Evidence

Studies meeting the criteria for inclusion in this report were assessed for their methodological quality using the Scottish Intercollegiate Guideline Network (SIGN) level of evidence system[2]:

Table 2. SIGN level of evidence

1++	High quality meta analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies High quality

[2] Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/

	case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

3 Results

3.1 Study selection

One RCT and two cases series reports met the inclusion criteria. These studies and the quality of their study design are presented in Table 3 below. Further detail of these studies and the details of the critical appraisal can be found in Appendix 2 at the end of this report. Patient cohorts in all these studies had CRPS-1, which was described as RSD in the case studies.

3.2 Quality Assessment

Within and between the three studies there was variability. The studies had low numbers of participants (n =16 – 29). Within the groups of included participants the effect of pamidronate on treating CRPS was looked at in different sites (lower limb and upper limb), at different stages of CRPS (pseudo-inflammatory compared to ischaemic), and CRPS arising due to traumatic and non-traumatic injuries. Within all studies the participants' use of other pain regimens was kept stable[4] or stopped[11, 12] for the duration of the studies to avoid any other additive (further pain reduction or false positive) effects.

Between the studies the predominant difference was the dose of pamidronate used. The two case-series (lower quality study design) administered pamidronate at a much higher dose (cumulative doses were 151 ± 39mg and 180mg) delivered over three infusions compared with the RCT (one infusion of 60mg). There were differences within the cohorts that were used, including a mix of upper and lower limb cases of CRPS; participants at different stages of CRPS (pseudo-inflammatory compared to ischaemic phase); and differences in how the effects of pamidronate were measured, and when they were measured after infusion. Two studies used the visual analogue scale (VAS) as an outcome measure but other measures varied between groups. Within the articles, outcomes for upper limb and lower limb CRPS sites were grouped together.

The quality of studies included in this report was appraised to be "moderate" and "low". This was due to the study designs (moderate for the RCT and low for the case-series) and low sample sizes. Further detail can be found in Appendix 3 at the end of this report.

Table 3. Brief outline of included studies for efficacy of pamidronate infusion in CRPS

Author	Study design	Pamidronate infusion details	CRPS Details	Outcomes	Level of evidence
Robinson et al, (2004)	Single-centre, double-blinded, randomised, placebo-controlled trial	Single IV infusion of pamidronate or placebo: Dose: 60mg Placebo: Saline infusion	Diagnosis: International Study for the Study of Pain (ISAP) criteria Cohort Lower limb = 13 Upper limb = 14 Disease duration: 2 months – 6 years Treatment group: n = 14 Placebo: n = 13	Measured at baseline then 1 and 3 months Visual analogue scale (VAS) scores Global assessment of disease severity SF-36 quality of life health survey	1 -
Cortet et al, 1997	Case-series (described by study as an open	Three sessions of IV infusions delivered over 3 hours on	Diagnosis: Doury's criteria CRPS sites: ankle (n = 10), hand	Measured on first day of perfusion, then at: 1 week, 1, 2,3 and 9 months VAS	3 -

	prospective study)	consecutive days at: 1mg/kg/day Total dose: 151 ± 39mg (mean ± SD)	(n=3), hip (n=2), knee (n=2) and shoulder (n=1) N = 16 in pseudoinflammatory stage, n = 7 in ischaemic phase	Pain verbal scale (PVS) EVS: global assessment of efficacy of treatment	
Kubalek et al, 2001	Case-series	Three sessions of IV infusion at a dose of 60mg (cumulative dose of 180mg)	Diagnosis: Doury's criteria N = 29 patients with CRPS Upper limb: 58.6% Lower limb: 41.4% Duration of disease: 42 ± 39 wks (range 2 – 163 wks)	Conducted on Day 15 and 45 post infusions Treatment success: if pain disappeared Increased range of motion of affected area of more than 20^{o} compared to pre-treatment	3 -

3.3 Visual Analogue Scale (VAS) findings

The RCT[4] and one of the case series[11] used the VAS as an outcome measure to determine the effectiveness of pamidronate infusions (main findings are outlined in Table 4 below). Significant differences were seen between the treatment and control group in the RCT at 3 months but not at 1 month. In the case series, there was a significant decrease in scores seen at day 30, which had decreased further by 9 months after infusion.

Table 4. Outcomes: Visual Analogue Scale scores

Study	Main finding
Robinson et al, 2004 (RCT)	- No difference between control and treatment: before pamidronate given, at 1 month post pamidronate infusion - Significant difference (P = 0.026) seen between control group and treatment group at 3 months, with treatment group having a lower median VAS score - The biggest change in VAS score in the treatment group was also seen at 0 – 3 months (P = 0.048) - The interquartile range between the control and treatment groups are similar
Cortet et al, 1997 (Case Series)	- No control group in this study - Significant decrease in score (from 77 to 57) seen between Day 0 and Day 30 post-infusion (p = .0002) and decreased further (to 53) by 9 months (p = .00003 when compared to Day 0). (Graph of VAS in Appendix 3)

3.4 Functional assessment scores

Functional improvement was assessed in two of the studies using different measures (see Table 5 below). Function was measured using a general physical health questionnaire SF-36 (Robinson et al, 2004) or by using specific range of movement parameters[12]. Both showed functional improvement after pamidronate infusion.

Statistically significant improvement in function was seen at 45 days in the case-series study[12] and at 3 months for the RCT[4].

Table 5. Outcomes: Functional assessments

Study	Main finding
Robinson et al, 2004 (RCT)	- Participant self-reported physical health status questionnaire SF-36 was used in this study - SF-36 was documented at baseline, 1 and 3 months - Participants in the treatment group had higher scores than the control group (P = 0.047) at 3 months (the higher the score indicates less disability)
Kubalek et al, 2001 (Case Series)	- This case series looked at functional improvement (range of movement more than 20^{o} compared to range before treatment) on day 45 and delay of functional improvement - Results showed 45 days after infusion 25 patients (86.2%) pain disappeared and functional improvement was seen in 14 out of 20 (70%) of patients - Functional improvement was faster in younger patients (ρ = -0.459; P = 0.0031), there was a larger number of traumatic cases in younger patients - Functional improvement was significantly faster in post-traumatic cases (16.9 ±9.7 days)

3.4.1 Adverse / side-effects

All three studies reported adverse events / side-effects as seen in Table 6 below. Some of the reported side-effects were similar: influenza type symptoms, fever, shivers, and nausea. Two of the studies[4, 11] reported that these effects were resolved within 48 hours[4], or within 4 weeks[11] .

Table 6. Outcomes: Adverse / side-effects

Study	Reported effects
Robinson et al, 2004 (RCT)	- Influenza type symptoms (n = 5 in treatment group, n = 2 in control) - Mild infusion site reactions (erythema, discomfort) n = 2 in treatment group - All symptoms resolved in 6 – 48 hours
Kubalek et al, 2001 (Case Series)	Seen in 20.7% of cases (n = 6), these included: - *Fever (n = 6)* - *shivers (n = 5), and* - *diarrhoea (n = 3).*
Cortet et al, 1997 (Case Series)	Seen in 60.8% (n = 14) of cases, these included: - *Transient fever >38^{o}C (n = 6)* - *Hypocalcaemia (n = 3)* - *Venous irritation (n = 2)* - *Nausea (n = 1)* - *Transient hypertension (n = 1)* - *Leucopenia with neutropenia (n = 1)* *All symptoms disappeared within 4 weeks without added intervention*

3.5 Other pain regimens during course of study

The two case studies reported that other analgesics or non-steroidal anti-inflammatory drugs (NSAIDS) were not authorised for the duration of the studies. One study also "forbade" the use of physical therapy and other medication known to be effective for RSD. In the RCT analgesics were allowed but restricted (See Table 7 below), and doses were held stable throughout the duration of the study.

Table 7. Other pain regimens present during course of study

Study	Main finding
Robinson et al, 2004 (RCT)	- Background analgesia continued throughout the study, and doses were held stable throughout the treatment period - Analgesia included: paracetamol (4g/day), codeine phosphate (120 – 180mg/day as monotherapy or with paracetamol) and paracetamol (325mg)/dextropropoxyphene (50mg) combination (up to 8 per day)
Cortet et al, 1997 (Case Series)	- Use of analgesics or NSAIDS forbidden - Medications known as effective for RSD such as griseofulvin, betablockers and steroids not allowed for duration of study - Physical therapy forbidden
Kubalek et al, 2001 (Case Series)	- Treated with pamidronate after failure of classical medical treatment for at least 14 days - Use of NSAIDs, calcitonin, steroids and infiltrations not authorised during study

4 Discussion

4.1 Nature and quality of evidence

Three studies were critically appraised, one RCT and two case-series. Within and between the studies there was variability in the progression of CRPS, anatomical site of CRPS, the dose of pamidronate, the length of time the effect of pamidronate was measured for and how the pain and function were assessed between studies after the infusion. All studies presented results that showed pamidronate decreased the effect of CRPS (decreased pain scores, increased range of motion around the affected joint). However due to variability within and across the studies it is difficult to definitively predict the effect pamidronate would have for a specific cohort of patients.

The RCT provided the highest quality evidence compared to the case-series due to its study design: the crucial difference between the RCT and the case series is that the RCT compared the effects of pamidronate against a placebo infusion of saline, whereas the two case series did not. This means the case series were unable to conclude whether any changes were due to the pamidronate infusion or natural progression of the participants' condition, thus providing a lower level of evidence.

The RCT (Robinson et al, 2004) was deemed to have a moderate level of evidence (SIGN level: 1-). Evidence was deemed moderate due to the small sample size (n=27) and variability within the cohort. However it is noted the RCT was well-designed. Participants were recruited consecutively and although 13 of the original 40 participants declined to participate in the study (See Appendix 3), the final group of participants was randomly placed into either treatment or placebo (similar volume of saline-only used for infusion) group, and participants and investigators were blinded. The variability seen within the results could be due to the variable nature of symptoms, sites and disease state of CRPS among the participants included in the study. It should also be noted that all other analgesics the participants used to control pain were kept constant during the duration of the study. The combination of low sample size, variability and good study design were all taken into account when considering level of evidence.

The case series that were found each followed a cohort of participants over a specific period of time (45 days, and 9 months respectively) and did not have a comparison / placebo group. Both studies stopped other types of pain management. However as these were case series any results presented could be a placebo effect from natural progression or reductions in CRPS symptoms due to other unknown reasons rather than because of the pamidronate infusion. Due to these issues, case-series including the two included studies are appraised to have low quality of evidence.

4.2 Limitations

The main limitation of this report is the paucity of studies around the efficacy of pamidronate for the treatment of CRPS-1. Searches of the conventional databases, and also hand searching of guidelines, revealed only the Robinson et al (2004) RCT and the Kubalek et al (2001) case-series that are included within this report.

As discussed in section 4.1 above, two of the predominant limitations of the studies included in this report were the small sample sizes and variability within the study cohorts. In all the studies, results for the upper limb and lower limb were analysed together, as were the results of participants who had different stages of CRPS, or CRPS arising from traumatic and non-traumatic events. It is possible these were grouped together due to the small sample sizes; however, overall statistically significant decreases in pain and increases in function were found after pamidronate use.

One other limitation that should be noted is that the evidence critiqued for this review was for CRPS-1 and does not cover CRPS-2.

4.3 External peer-review comments

An external peer-review was conducted by a Professor of Medicine at the University of Auckland and a Fellow of the Royal Society of NZ. This professor was approached to do the external peer-review because of his expertise in bone and metabolic and genetic bone diseases, and from that has multiple publications in international journals of the efficacy of bisphosphonates (infusion and oral) in different bone-related disorders.

Main peer-review comments (truncated):

"… *everyone believes all aminobisphosphonates work through the same mechanism, so it seems to me that the two important studies are the RCTs in CRP-1; Robinson et al (2004) with Pamidronate and Varenna et al (2013) with Neridronate. I think you need to try and (meta)analyse these together - this would provide the most robust data on the effectiveness of BPs in CRP. The fact that we don't have Neridronate in Aotearoa is of lesser importance.*"

4.3.1 Findings from directly comparing results of Varenna et al (2013)[7] and Robinson et al (2004)[4]

A meta-analysis was not conducted, however the results for these two studies are represented against each other Table 8 and Table 9 in Appendix 4 at the end of this document. The main findings were:

Demographics, and details of bisphosphonate infusion in studies:

- Main difference was the bisphosphonate used and the amount of bisphosphonate:
    - Pamidronate: Single IV infusion of 60mg
    - Neridronate: 4 x 100mg over 10 days via IV infusion
- Outcomes used to measure efficacy of bisphosphonate was similar (VAS, SF-36)
- Similarities in initial time points efficacy was measured - 1 month, 20 and 30 days
- Varenna et al (2013) had a larger cohort (n = 82; treatment = 41, placebo = 41)
- Both studies grouped upper limb and lower limb results together

Main results:

- Both studies showed decreased VAS scores
- Both studies showed increased SF-36 scores (higher scores signify a positive response)
- Both had similar adverse effects (fever, influenza type symptoms) that resolved in 1 – 3 days without further intervention
- Differences in other pain regimens
    - Robinson et al (2004): Background analgesia were continued and held stable throughout the treatment period. Included paracetamol, codeine phosphate, and paracetamol combined with dextropropoxyphene
    - Varenna et al (2013): Not stated that regimens were kept stable. NSAID use monitored as a measure of effects of neridronate on pain - All patients receiving treatment, and 45% of placebo discontinued symptomatic drugs in two weeks of receiving infusion.

4.3.2 Summary

These RCTs used similar measures to determine the efficacy of the bisphosphonate they used in their study. These bisphosphonates have a similar molecular structure and are thought to work through similar underlying physiological mechanisms. Both showed the bisphosphonate decreased pain scores, and increased functional scores.

5 Conclusion

This report shows there is a paucity of studies that have investigated the effectiveness on pamidronate on people with CRPS. Clinical guideline or insurer policies that have made statements regarding pamidronate almost all (except Aetna) reference Robinson et al (2004), the only RCT that was found in the search by two ACC reviewers. Two other case-series were also included within this report, although these provided a lower level of evidence due to their study design.

The RCT has been critiqued to have a moderate level of evidence due to size and variability within the cohort, however it is a well-designed RCT. Due to the paucity of studies and variability it is difficult to make a definitive recommendation with regard to the use of pamidronate for the treatment of CRPS; however it should also be taken into account that guidelines that recommend the use of pamidronate have derived their recommendations from the same evidence sources. Also of relevance is that other bisphosphonates that have similar molecular structures to pamidronate, used similar outcome measures[7] which also showed decreases in pain scores and increased functional scores in participants with CRPS-1. This indicates that pamidronate and similarly structured bisphosphonate have positive outcomes in people with CRPS-1 after one infusion.

Overall the RCT and case-series show that, within variable cohorts, pamidronate does reduce pain scores and helps improve function. Although the case-series both used much higher doses of pamidronate, a reduction was still seen in the RCT which used a much lower dose. It should be noted that adverse effects of pamidronate (Table 6) were reported to largely resolve without any further intervention. In general pamidronate infusion appears to be effective in decreasing pain in people with CRPS-1 at a lower dose of 60mg. Although the best evidence for this comes from a single RCT, other guidelines have used this evidence to support their recommendations (see Table 1).

A preliminary recommendation for IPM item IN60: Pamidronate infusions, based on the available literature, is:

- **Purchase on a case by case basis**

6 References

1. Woo S-B, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. Annals of internal medicine. 2006;144(10):753-761.

2. Albazaz R, Wong YT, Homer-Vanniasinkam S. Complex Regional Pain Syndrome: A Review. Annals of Vascular Surgery. March 2008/April 2008;22(2):297-306.

3. O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews. Cochrane Database of Systematic Reviews. 2013;2013(4).

4. Robinson J, Sandom J, Chapman PT. Efficacy of pamidronate in complex regional pain syndrome type I. Pain Medicine. 2004;5(3):276-280.

5. Harden RN, Oaklander AL, Burton AW, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines. Pain Medicine. 2013;14(2):180-229.

6. Mailis A, Taenzer P. Evidence-based guideline for neuropathic pain interventional treatments: spinal cord stimulation, intravenous infusions, epidural injections and nerve blocks. Pain Research & Management: The Journal of the Canadian Pain Society. 2012;17(3):150.

7. Varenna M, Adami S, Rossini M, et al. Treatment of complex regional pain syndrome type I with neridronate: A randomized, double-blind, placebo-controlled study. Rheumatology (United Kingdom). March 2013;52(3):534-542.

8. Koivisto K, Kyllonen E, Haapea M, et al. Efficacy of zoledronic acid for chronic low back pain associated with Modic changes in magnetic resonance imaging. BMC Musculoskeletal Disorders. 04 Mar 2014;15(1).

9. Laslett LL, Doré DA, Quinn SJ, et al. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. Annals of the Rheumatic Diseases. February 21, 2012 2012;71(8):1322-1328.

10. Pappagallo M, Breuer B, Lin HM, et al. A pilot trial of intravenous pamidronate for chronic low back pain. Pain. January 2014;155(1):108-117.

11. Cortet B, Flipo RM, Coquerelle P, Duquesnoy B, Delcambre B. Treatment of severe, recalcitrant reflex sympathetic dystrophy: assessment of efficacy and safety of the second generation bisphosphonate pamidronate. Clinical Rheumatology. Jan 1997;16(1):51-56.

12. Kubalek I, Fain O, Paries J, Kettaneh A, Thomas M. Treatment of reflex sympathetic dystrophy with pamidronate: 29 cases. Rheumatology. Dec 2001;40(12):1394-1397.

13. Brunner F, Schmid A, Kissling R, Held U, Bachmann LM. Biphosphonates for the therapy of complex regional pain syndrome I – Systematic review. European Journal of Pain. 2009;13(1):17-21.

7 Appendices

7.1 Appendix 1: Search Strategy

7.1.1 a.) Pamidronate in CRPS

Search strategy: *Medline, Pre-Medline, Embase, AMED & Ovid Nursing Database searched 7 Sept 2015*

1. pamidron$.mp.
2. (Aredia or Pamimed).mp.
3. (Complex Regional Pain Syndrom$ or reflex sympathetic dystrophy or causalgia or CRPS or RSD).mp.
4. (1 or 2) and 3
5. remove duplicates from 4
6. limit 5 to human
7. limit 6 to humans

7.2 Appendix 2: Bisphosphonate infusions for the treatment of chronic pain

The purpose of these appendices is to present a brief overview of the evidence for other members of the bisphosphonate family that have been delivered as an infusion in chronic pain syndromes. A restricted search was conducted that was a direct continuation of the original search done for the ACC IPM guidance in 2005.

The intent of this section is to provide additional information on the efficacy of other classes of bisphosphonates in other pain pathologies at the request of the ACC pharmaceutical advisor. As it includes bisphosphonates that are not available in New Zealand, or not used for pain as an infusion, or are not used to treat CRPS, it does not meet the original research question for this report. For these reasons this section has been made into an appendix.

7.2.1 Methodology

7.2.1.1 Search Strategy

A systematic search was conducted over multiple databases using search terms as described below by two ACC research advisors.

A search was conducted in March 2015 across the following databases:

- AMED (Allied and Complementary Medicine) <1985 to May 2014>
- Embase <1988 to 2014 May 16>
- Pre-MEDLINE
- Ovid MEDLINE <1946 to Present>,
- Google scholar
- Ovid Nursing Database

7.2.1.2 Inclusion and Exclusion Criteria

Inclusion Criteria

- Types of studies: Systematic reviews, randomised control studies
- Types of participant: pain disorders
- Types of interventions: bisphosphonate infusion
- Types of comparison: placebo,
- Types of outcome measures: visual analogue scale.

Exclusion Criteria

- Study designs other than systematic reviews and RCTs
- Studies on pamidronate use in CRPS
- Grey literature (eg conference proceedings, non peer-reviewed literature), literature reviews
- Animal or laboratory studies
- Non-English studies

7.2.2 Study selection

Four RCTs met the inclusion criteria for this part of the report. A brief overview of these articles and the quality of their study design are presented in Table 8 below. Further detail of these studies and the details of the critical appraisal can be found in Appendix 3.

A Cochrane review was found that provided a summary of evidence from Cochrane and non-Cochrane systematic reviews on therapeutic interventions for CRPS[3]. Within this review two systematic reviews were critiqued with regard to bisphosphonates: Brunner et al, 2009 and Chuvineau, 2005. As Chuvineau (2005) is written in French it was excluded. A description of Brunner et al (2009)[13] can be found in Section 6.3.3 of this report. Two of the primary studies that were included by Brunner et al (2009) for bisphosphonate infusions have been included in the original IPM 2005 guidance (Varenna et al, 2000 and Adami et al, 1997). The other RCT, Robinson et al, 2004 is included in the main critical appraisal of this report. Due to the focused research question it was decided to critique the relevant primary studies and not the systematic reviews and Cochrane review.

7.2.3 Quality assessment

The RCTs were critiqued as providing moderate to high levels of evidence. The patient cohorts were variable between the studies, and included disorders that are usually out of the scope of ACC (Knee osteoarthritis/OA). The placebos used across these studies were saline and delivered at a similar volume through an IV infusion. Different bisphosphonates were used between studies and further details of each study can be found in Appendix 3.

Of interest for this report, a dose response was conducted for pamidronate infusions in a cohort of patients with lower back pain[10]. This study showed that there was a significant decrease in pain intensity scores with a high dose of pamidronate (180mg).

Table 8. Overview of RCTs for bisphosphonate use for pain in other pathologies

Paper	Study design	Patient cohort	Bisphosphonate and Dose	Main findings	Level of evidence
Varenna et al, 2013[7]	Prospective, double-blind RCT	CRPS-1: Both sensory and vasomotor disturbances, oedema and functional impairment of hand or foot	Neridronate: 100mg (structurally similar to alendronate and pamidronate), given four times over 10 days. Infused in 500mL saline over 2 hours Vs Placebo	Continual decreasing in VAS scores at 40 days. Long-term follow-up showed effects lasted a few months after trial Some decreases in SF-36 (quality of life) scores.	1+
Koivisto et al, 2014[8]	Single centre, double blind RCT	Lower Back Pain with Modal changes	Zoledronate: Single IV infusion of 5mg in 100mL Saline over 15 min Vs Placebo	Decrease in LBP intensity after 1 month, however this decrease was not present at 12 months No conclusive results seen for modal changes Patients stated NSAID use decreased.	1-
Laslett et al, 2012[9]	Single centre, double-blinded, randomised placebo controlled RCT	Knee OA, Bone marrow lesions	Zoledronate: Single infusion of 5mg in 100mL Saline Vs placebo	ZA reduces knee pain at 6 months, but effect seems to have decreased at 12 months	1+
Pappagallo et al, 2014[10]	Randomised double-blind placebo controlled study. **Pilot study**	Centralised lower back pain Dose response examined	Pamidronate: Single infusion of 30, 60 or 90mg, or double infusion of 2 x 90mg (total 180mg dose, with 4 week period between) Vs Placebo	Significant decrease in pain intensity scores at 24hrs, 1, 2,3 months and 6 months with 180mg dose No significant differences seen for Oswestry disability index or quality of life scores. At 6 months the proportion of subjects using non-opioid analgesics decreased.	1-

7.2.4 Summary

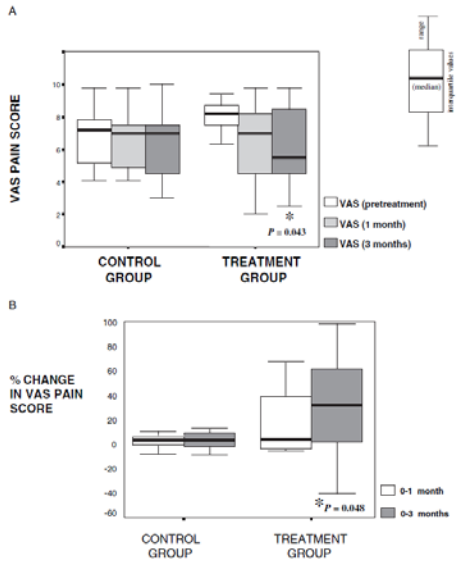
There is a paucity of high quality studies that have investigated the efficacy of bisphosphonates for the treatment of pain. Some of the patient cohorts that have been investigated have pain disorders that are out of scope for ACC. What these RCTs show is that bisphosphonates appear to reduce pain. However summarising the overall efficacy of bisphosphonates for use in pain disorders is difficult due to the variable nature of the studies. This includes different bisphosphonates at different doses, different patient cohorts, and different ways of measuring outcomes. The variability makes it difficult to come to a succinct conclusion for the efficacy of bisphosphonates for pain syndromes and construct recommendations for its use. Further randomised control trials are required and could be designed based on how bisphosphonate infusions might be used clinically.

7.3 Appendix 3: Evidence tables

7.3.1 Evidence Tables: Randomised control trials for Pamidronate infusions for CRPs

Study	Methodology	Outcomes & results	Paper grading[3]		ACC reviewer comments & evidence level
Robinson et al, (2004) [4] Pain Medicine, 5(3), 276 – 280 **Study design:** Single-centre, double-blinded, randomized, placebo-controlled trial **Research question:** To determine the efficacy of IV Pamidronate in CRPS-1 patients **Funding** Not stated	<u>Population demographics</u> N = 27 (18 female, 9 male, average age 45 years) Background analgesia continued throughout study, doses held stable through 3 month period (incl, codeine, paracetamol, and combinations. Patients and investigators blinded <u>CRPS diagnosis</u> Fufilled the international Association for the Study of Pain (IASP) criteria for CRPS Type I <u>Inclusion</u> Fulfilled the International Association for study of pain criteria for CRPS-1 Enrolled in study over 2 year period (1998 – 2000) <u>Disorder / Inclusion criteria</u> Lower back pain symptoms for at least 3 <u>Exclusion criteria</u> Not stated	<u>Demographics</u> 40 consecutive patients meeting criteria approached, 13 declined with main reason being concern of being randomised to the placebo arm. Lower limb: n = 13 Upper limb: n = 14 Disease duration: 3 months – 6 years Rx group: n = 14 Placebo: n = 13 <u>Adverse effects</u> 6 – 48 hours after infusions: Influenza-type symptoms, infusion site reactions (erythema) <u>Main Findings</u> SF-36: Rx group had significantly higher scores than those in placebo group.	Appropriate and focused question? Subjects to treatment groups randomized? Adequate concealment method Subjects and investigator kept "blind" Treatment and control groups similar at the start of trial Only difference between groups is treatment under investigation Relevant outcomes are measured in a standard, valid and reliable way Percentage of individuals or clusters recruited to each treatment arm that dropped out of the study All subjects analysed in groups to which they were randomly allocated (intention to treat analysis) If study performed across multiple sites, results are comparable for all sites Are results of RCT directly applicable to Bisph use for ACC clients?	Y Y CS Y Y Y Y 0 Y NA CS	**Small sample size** **Huge variation in the results seen in Figure 1 despite significant statistics being found although medians are reported** **No clarity on exclusion criteria** **Distribution of UL or LL in Rx and placebo groups unknown** **No dropouts, however 32.5% of original number of patients who met criteria declined being included as did not want to be placed in placebo group.** **Overall well conducted RCT, however the effects of pamidronate are not clear. The study does show that there is an effect of pamidronate on VAS scores, however this is variable. The study has been given a lower evidence level for RCTs due to the small sample**

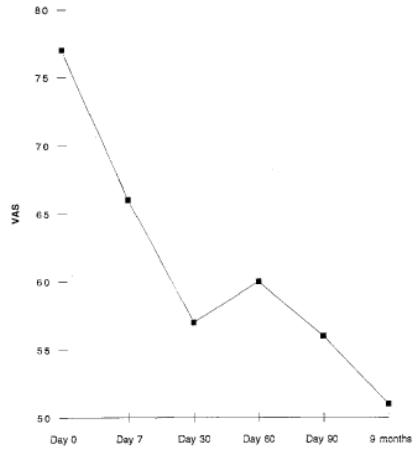
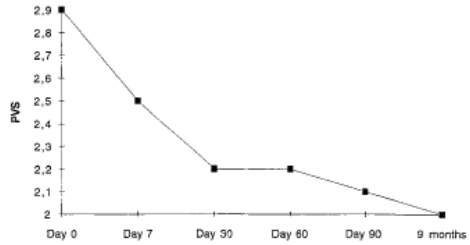
[3] Y = yes, N = no, NA = not applicable, ? = can't say (information is missing or unclear)

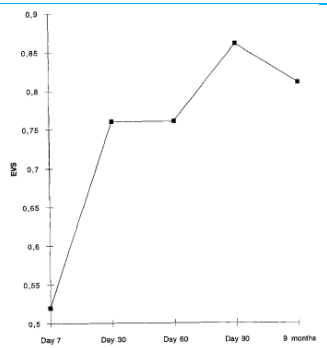
	Type of bisphosphonate: Single IV infusion of 60mg Pamidronate or placebo Outcome measures *(baseline, 1 and 3 months)* VAS scores, patients global assessment of disease severity scores, SF-36	**Table 1** Patient's global assessment of disease severity Pretreatment / 1 month / 3 months Control Group Median 5.8 / 4.6 / 5.3 Interquartile range (4.1–7.8) / (4.0–7.6) / (4.0–7.0) Treatment Group Median 7.6 / 6.9 / 5.3 Interquartile range (5.4–9.3) / (5.0–8.4) / (4.5–8.0) *P* value 0.11 / 0.23 / 0.026 Patients were asked to rate the severity of their condition on an arbitrary scale (0–10; 0 = no disease activity, 10 = maximal disease activity) at pretreatment and at 1 and 3 months posttreatment.  Author conclusions: Pamidronate may be a useful treatment option in the management of patients with CRPS-1. Although treatment response was variable, the majority of patients improved.			**size and the variable nature of the results.** **Level of evidence: 1-**

7.3.2 Outline of Case-series publications for pamidronate infusions in CRPS

Study	Methodology	Outcomes & results	Paper grading[4] (Using combination of SIGN criteria for diagnostic studies, and CEBM criteria for prognosis)		ACC reviewer comments & evidence level
Cortet et al, 1997 *Clinical Rheumatology, 16, pg 51 - 56* **Study design:** Case-series, Study describes it as an open prospective study **Research question:** To assess the efficacy and the safety of pamidronate in recalcitrant reflex sympathetic dystrophy (RSD). **Funding** Not stated	<u>Population demographics</u> N = 10 women N = 13 men Mean age: 44± 11 years <u>Inclusion</u> Had disease for over 3 months (mean duration was 15±13 months, median 13 months)with previous inefficacy of calcitonin therapy seen in persistence of severe pain (measured on VAS) Use of NSAIDs or analgesics forbidden during study Physiotherapy forbidden Minimal period between last treatment of RSD and administration of pamidronate was 15 days <u>Diagnosis of CRPS</u> Doury's criteria <u>Dose:</u> 1mg/kg/day for 3 consecutive days due to adverse effects, diluted in	<u>Demographics</u> RSD (CRPs) sites: Ankle (n=10), foot (n=7), hand (n=3), hip (n=2), knee (n=2) and shoulder (n=1). Traumatic in 17 cases 11 cases previously treated unsuccessfully with sympathetic blockades 16 cases pseudo-inflammatory stage 7 cases in ischaemic phase 5 characterised by non-detailed psychic disorders <u>Total dose of pamidronate</u> 151 ± 39mg (mean ± SD) <u>Adverse effects</u> Observed in 14 patients: Transient fever >38 (n=6) Hypocalcaemia (n = 3) Venous irritation (n = 2) Nausea (n = 1) Transient hypertension (n = 1) Leucopenia with neutropenia (n = 1) All disappeared within 4 weeks without	Is the paper relevant to the key question?	Y	**Variable study population that included patients with CRPs that arose from a mixture of injuries, injury sites and at different stages of the disease.** **Study methodology showed there were small decreases in pain with VAS (decrease of about 2.7 mm) and verbal scores (0.9), and increases within efficacy scale that was gradual to 9 months.** **Study did not present any measures of variability only P-values from Wilcoxon paired tests.** **Due to study design cannot exclude placebo effect or spontaneous movement of the disease** **Based on study design and variable population:** **Level of evidence: 3-**
			A consecutive or random selection of patients is enrolled	CS	
			Inappropriate exclusions are avoided	Y	
			Patients and settings match the key question	Y	
			The sample of patients were assembled at a common point at the course of their disease?	N	
			Patient follow-up sufficiently long and complete?	Y	
			Were outcome criteria either objective or applied in a 'blind' fashion?	Y	
			If a threshold is used it is pre-specified	CS	
			Is the interpretation similar to that used in practice with the target population?	Y	
			Condition is defined by how it is defined in the target population of the guideline	Y	
			All patients recruited into the study are included in the analysis	Y	

[4] Y = yes, N = no, NA = not applicable, ? = can't say (information is missing or unclear)

	500mL of isotonic glucose, administered via IV over 3 hours <u>Outcome measures</u>: Measured on first day of perfusion, 1 week, 1 month, 2 months, 3 months, 9 months VAS: Visual analogic scale for pain PVS: Pain verbal scale EVS: Global assessment of efficacy of treatment	any added intervention <u>Main Findings</u> Visual Analogue Scale  *Fig. 1*: Evolution of verbal analogic scale (VAS) Pain Verbal Scale  *Fig. 2*: Evolution of pain verbals scale (PVS) Efficacy verbal scale	Is the assessment applicable to the target population?	Y	

		 *Fig. 3:* Evolution of efficacy verbal scale (EVS) <u>Author conclusions:</u> Results suggest an efficacy of pamidronate in recalcitrant RSD. Double-blind placebo controlled studies are required to back up these preliminary results.			

Study	Methodology	Outcomes & results	Paper grading[5] (Using combination of SIGN criteria for diagnostic studies, and CEBM criteria for prognosis)		ACC reviewer comments & evidence level
Kubalek et al, 2001 *Rheumatology, 40: 1394 - 1397* **Study design:** *Case series* **Research question:** *To evaluate the efficacy of treatment with pamidronate in reflex sympathetic dystrophy (RSD) refractory to previous treatment* **Funding** *Not stated*	<u>Population demographics</u> N = 29 patients (seen in 1993 – 1999) 10 men Ave age 53.0±14 yrs <u>Inclusion</u> <u>Diagnosis</u> Doury's criteria All patients complained of pain associated with allodynia and or hyperpathia, tenderness and reduced range of motion, symptoms in an area much larger than the primary injury and symptoms aggravated by physical activity of the affected extremity. Bone scintigraph suggestive of RSD (CRPs) <u>Dose:</u> Daily dose of 60mg in 500mL 5% glucose solution over a period of 3 consecutive days (cumulative dose of 180mg) Not using other pain treatments during course of trial	<u>Demographics</u> Upper limb 58.6% cases Lower limb 41.4% cases Duration of disease: 41.89±38.9 wks (range 2 – 163 wks) TABLE 2. Characteristics of the 29 patients treated with pamidronate Localization: Shoulder 51.7%, Hand 6.9%, Knee 13.8%, Foot 31% Aetiology: Stroke 3.4%, Diabetes 34.5%, Trauma 31%, Hyperthyroidism 3.4%, Drugs 10.3%, Cancer 10.3%, Idiopathic 6.9% <u>Adverse effects</u> In 6 cases: Fever N = 6, Shivers n = 5, diarrhoea n = 3. <u>Main Findings</u>	Is the paper relevant to the key question?	Y	**Only considered cases of refractory RSD (had previous treatments), only looked at total disappearance of pain and improvement in range of movement which may account for some of the NS statistical analyses** **Participants at wide range of stages of disease (2 – 163 weeks)** **Mixture of ages, sites (although mostly shoulder) and aetiologies. Mixture of previous treatments including calcitonin, NSAID, steroids, Griseofulvin, B-blockers, infiltration, physical.** **Level of evidence: 3-**
			A consecutive or random selection of patients is enrolled	Y	
			Inappropriate exclusions are avoided	Y	
			Patients and settings match the key question	Y	
			The sample of patients were assembled at a common point at the course of their disease?	N	
			Patient follow-up sufficiently long and complete?	Y	
			Were outcome criteria either objective or applied in a 'blind' fashion?	N	
			If a threshold is used it is pre-specified	Y	
			Is the interpretation similar to that used in practice with the target population?	Y	
			Condition is defined by how it is defined in the target population of the guideline	Y	
			All patients recruited into the study are included in the analysis	Y	
			Is the assessment applicable to the target population?	Y	

[5] Y = yes, N = no, NA = not applicable, ? = can't say (information is missing or unclear)

	Outcome measures: Evaluated on days 15 and 45 Rx successful if pain disappeared completely (analgesia stopped). Function improvement if increase of range of motion of more than 20^0 compared to before	TABLE 3. Clinical evolution after pamidronate treatment 		Pain disappearance on day 45		Delay of pain disappearance (days)		Functional improvement on day 45		Delay of functional improvement (days)	
---	---	---	---	---	---	---	---	---
	(%)	P	(mean ± s.d.)	P	(%)	P	(mean ± s.d.)	P
Sex								
Men	66.7		27.8 ± 16		50		32.5 ± 11.3	
Women	94.4	NS	17 ± 12.1	NS	77.8	NS	27.8 ± 20.4	NS
Localization								
Upper limb	85.7		21 ± 14.4		64.3		29.5 ± 21.6	
Lower limb	86.7	NS	19 ± 14.9	NS	71.4	NS	28.3 ± 14.2	NS
Aetiology								
Post-traumatic	77.8		16.9 ± 13.5		77.8		16.9 ± 9.7	
Other	88.9	NS	21.3 ± 16.7	NS	65	NS	34.9 ± 18.1	0.04
Total	86.2		19.96 ± 14.4		70		28.9 ± 18.3	| Author conclusions: Pamidronate appeared to be effective in treatment of refractory RSD, however this needs to be confirmed by a controlled placebo study			

7.3.3 Evidence tables: Systematic Reviews (not included in the final evidence synthesis)

Study	Methodology	Outcomes & results	Paper grading[6]		ACC reviewer comments & evidence level
O'Connell et al, 2013 [3] **Study design:** Overview of reviews **Research question:** Summary of evidence from Cochrane and non-Cochrane SR on therapeutic interventions for CRPs and to direct readers to the available reviews **Funding** Not stated	<u>Number of studies:</u> Six Cochrane and 13 non-Cochrane systematic reviews <u>Literature search:</u> Systematic search of: Cochrane Database of SRs, Database of Abstracts of Reviews of Effects (DARE), Ovid MEDLINE, Ovid EMBASE, CINAHL, LILACS and PEDro <u>Inclusion criteria:</u> All Cochrane reviews of RCTs that assessed the effects of interventions used to reduce pain or disability in people with CRPs. Cochrane and non-Cochrane systematic reviews, based on grading using AMSTAR tool and whether a comprehensive literature search was performed >18 years with CRPS or alternative descriptor <u>Exclusion criteria:</u> Diagnoses other than CRPS <u>Characteristics of included studies:</u> Cochrane reviews had better	This study provides an overview of different interventions that can be used for the treatment of complex regional pain syndrome (CRPs). With regard to Bisphosphonates the review discusses two non-Cochrane SRs: Brunner 2009 and Chuvineau 2005. The two reviews investigate the effect of Alendronate and pamidronate with placebos. The RCTs had small sample sizes and assessed as being of moderate quality. *Both of these studies are reviewed below* Summary graded papers using GRADE criteria Outlined adverse effects from the use of IV pamidronate (influenza symptoms, fever with clondronate, asymptomatic hypercalcaemia. <u>SR conclusions</u> Low quality evidence that bisphosphonates may be effective for treating pain in CRPS-1. Graded down because of low sample size, pain scoring systems used in the studies. Bisphosphonates may effectively reduce pain when compared with placebo at least in the short term	Clearly defined research question	Y	**This Cochrane summary is a document that covers different pain interventions for CRPs.** **It is a high quality review of low quality evidence.** **Level of evidence: 1+**
			Two people selected studies & extracted data	?	
			Comprehensive literature search carried out	Y	
			Authors clearly state how they limited review by publication type	Y	
			Included & excluded studies listed	Y	
			Characteristics of included studies provided	Y	
			Scientific quality of included studies assessed & documented	Y	
			Scientific quality of included studies assessed appropriately	Y	
			Appropriate methods used to combine individual study findings	NA	
			Likelihood of publication bias assessed		
			Conflicts of interest declared	CS	
			Are results of SR directly applicable to Bisphosphonate use for ACC clients?		

[6] Y = yes, N = no, NA = not applicable, ? = can't say (information is missing or unclear)

	methodological quality than non-Cochrane reviews.				

Study	Methodology	Outcomes & results	Paper grading[7]		ACC reviewer comments & evidence level
Brunner et al, 2009 [13] European Journal of Pain, 13, p 17 - 21 **Study design:** SR of RCTs **Research question:** To perform a SR of all RCTs to assess the benefit of bisphosphonates in the Rx of CRPS-1 patients with bone loss **Funding** Not stated	Number of studies: 4 RCTs included Searches retrieved 1,767 records, of which 16 potentially relevant. 12 were excluded, however these details not reported Literature search: Medline (Pubmed), Embase (Ovid interface to 2007), Cochrane Central Register of Controlled Trials (2007, issue 2), screening bibliographies of all included studies Inclusion criteria: RCTs comparing BISph with placebo with the goal of improving pain function and QOL of people with CRPS-1 No language restrictions Exclusion criteria: Not provided	Demographics: N=118 across studies. <30 in study arms Mean age: 51.7 years Site of CRPS-1 Upper limb: n=30 Lower limb: n = 89 Trauma (n=38) and Fracture (n=28) most frequent initiating events N=3 were treated intravenously. BISph used: Alendronate: IV and orally IV: 7.5mg Pamidronate: IV 60mg, single infusion Clondronate: IV 300mg day for 10 days Duration: 3 days – 8 weeks between studies Outcome measures: VAS, tenderness, ROM, Hydroxyprolin/creatinine score	Clearly defined research question	Y	Description of how papers were graded are explained and are appropriate and performed by 2 independent reviewers, the scale provided though is not a validated tool (eg, SIGN or GRADE etc). Restrictions and scope of review are good Methods of how pain scores are pooled and explanations of what this means are unclear Details of excluded studies not included Three of the four RCTs were IV administrated Bisphosphonate compounds. Two of these (Adami, 1997 and Varenna et al, 2000) were included in the 2005 IPM guideline. Robinson et al, 2004 was not included thus this SR is included for this review. **Level of evidence: Low**
			Two people selected studies & extracted data	Y	
			Comprehensive literature search carried out	Y	
			Authors clearly state how they limited review by publication type	Y	
			Included &excluded studies listed	N	
			Characteristics of included studies provided	Y	
			Scientific quality of included studies assessed & documented	Y	
			Scientific quality of included studies assessed appropriately	N	
			Appropriate methods used to combine individual study findings	CS	
			Likelihood of publication bias assessed	Y	
			Conflicts of interest declared	N	
			Are results of SR directly applicable to BISph use for ACC clients?	Y	

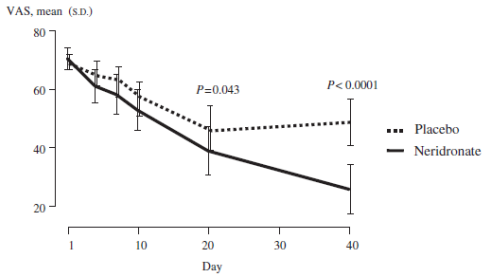
[7] Y = yes, N = no, NA = not applicable, ? = can't say (information is missing or unclear)

		SF-36 Side effects: Fever (alendronate), Asymptomatic hypocalcemia (clondronate), influenza symptoms and infusion site reaction (pamidronate) <u>Results from studies:</u> Some improvements in pain scores, ROM, physical function, <u>Study Quality assessment:</u> Moderate <u>SR conclusions:</u> Limited data reviewed show that Bisphosphonates have the potential to reduce pain associated with bone loss in patients with CRPS-1. Evidence not sufficient to recommend use in practice Treatment regimens should only be initiated with research protocols that clearly define exposures and involve standardised outcome assessments. Should also be based on a multidisciplinary approach than a single medication			**quality 1-**

7.3.4 Evidence Tables: Randomised Control Trials for Bisphosphonate infusions that are not pamidronate

Study	Methodology	Outcomes & results	Paper grading[8]	ACC reviewer

[8] Y = yes, N = no, NA = not applicable, ? = can't say (information is missing or unclear)

					comments & evidence level
Varenna et al, 2013 [7] Rheumatology 52(3), 534 - 542 **Study design:** Prospective double-blind randomised placebo-controlled study **Research question:** To test the efficacy of neridronate in patients with CRP-1 **Funding** Abiogen Pharma, SpA, Pisa, Italy. Authors stated no conflict of interest	<u>Population demographics</u> 82 patients (out of 84 referrals) recruited over 20 months from outpatient services of six Italian rheumatology centres **Characteristic** / **Neridronate (n = 41)** / **Placebo (n = 41)** / ***P* value** Age, mean (S.D.), years: 58.2 (12.7) / 57.0 (10.3) / 0.6 Gender, M/F, *n*: 16/25 / 13/28 / 0.6 Disease duration, mean (S.D.), weeks: 4.7 (4.1) / 5.0 (4.6) / 0.7 Precipitating event, *n* (%) Fracture: 11 (26.8) / 17 (41.4) / 0.2 Trauma: 10 (24.4) / 7 (17.1) / 0.5 Surgery: 5 (12.2) / 4 (9.8) / 0.9 Unknown: 15 (36.6) / 13 (31.7) / 0.8 Site, *n* (%) Upper limb: 8 (19.5) / 12 (29.3) / 0.4 Lower limb: 33 (80.5) / 29 (70.7) <u>Disorder</u> CRP-1 (sensory and vasomotor disturbance, oedema and functional impairment of hand or foot), diagnosed according to Budapest Criteria <u>Type of bisphosphonate:</u> IV infusion of 100mg Neridronate (structurally similar to alendronate and pamidronate) given four times over ten days, every third day starting from day 1 or placebo, infused in 500m l saline, infused over 2 hours At 50 days the former placebo patients were given open label the same regimen of neridronate <u>Outcome measures</u> Visual analogue scale, Clinical signs	<u>Outcomes measured</u> at Day 1 (first infusion), Day 10 (last infusion), 20 days, 40 days <u>Participants</u> Out of initial 82, 8 dropped out due to: adverse effects after initial infusion, consent withdrawal, and lack of post baseline measurement (efficacy). <u>VAS score results</u> Significant results seen at day 20 and 40  <u>SF-36 Results</u> **Domains and components** / **Difference between neridronate and placebo: Estimate** / **95% CI** / ***P* value** Physical functioning: 13.2 / 4.7, 21.8 / 0.003 Role limitations due to physical health: 19.1 / 4.3, 33.9 / 0.012 Role limitations due to emotional problems: 13.3 / −2.9, 29.5 / 0.107 Energy/fatigue (vitality): 3.5 / −3.1, 10.2 / 0.295 Emotional well-being (mental health): 13.6 / 6.7, 20.5 / 0.0002 Social functioning: 9.9 / 0.5, 19.3 / 0.039 Pain: 9.8 / 2.1, 17.4 / 0.013 General health: 1.2 / −4.6, 7.1 / 0.683 Physical component scale: 3.7 / 0.9, 6.5 / 0.009 Mental component scale: 4.9 / 1.2, 8.6 / 0.010 Data are expressed as least-square mean estimates with associated 95% confidence interval. Significant positive effects for most SF-36 results except general health, and energy + fatigue levels <u>Open phase extension</u> For cohort that originally were given	Appropriate and focused question?	Y	**Appears to be a higher dose of bisphosphonate compared to other studies?** **Time period effects measured over 40 days which is considerably shorter than other studies** **Results not reported for upper vs lower limb** **Unsure if this bisphosphonate is available in New Zealand** **Overall a well conducted focused RCT. However done over a much shorter time period compared to other papers in this review. Did briefly mention long-term follow-up effects but the details around this were not clear.** **Level of evidence: 1+**
			Subjects to treatment groups randomized?	Y	
			Adequate concealment method	Y	
			Subjects and investigator kept "blind"	Y	
			Treatment and control groups similar at the start of trial	Y	
			Only difference between groups is treatment under investigation	Y	
			Relevant outcomes are measured in a standard, valid and reliable way	Y	
			Percentage of individuals or clusters recruited to each treatment arm that dropped out of the study	9.7	
			All subjects analysed in groups to which they were randomly allocated (intention to treat analysis)	Y	
			If study performed across multiple sites, results are comparable for all sites	Y	
			Are results of RCT directly applicable to BISph use for ACC clients?	CS	

	and symptoms (oedema, pain, allodynia, hyperalgesia, SF-36, McGill Pain Questionnaire <u>Inclusion criteria</u> CRPS-1 of hand or feet, at least 18 years, had disease no longer than 4 months, spontaneous pain intensity of 50 – 100mm on VAS, three phase bone scintigraphy obtained <u>Exclusion</u> Pregnancy, hepatic, renal, endocrine haematological, cardiac, pulmonary or neurological diseases or routine lab abnormalities and prior Rx with bisphosphonates	placebo Main results show decreases in all assessments (VAS and SF-36 scores) except for mental component scale <u>Long-term follow-up</u> Conducted a few months after initial trial (number months not stated). Considered a separate study, preliminary findings (n=78) showed improvements from main study retained. Bone scintigraphy (n=36) showed complete normalisation of abnormal uptake. In n = 12 patients bone odema had disappeared. <u>Adverse effects</u> N=21 in neridronate, 12= placebo, complained of at least one effect. Polyarthralgia: 12 for neridronate, 5 placebo; Fever: 9 neridronate, 1 placebo, this disappeared after 3 days. No serious drug-related effects reported during study <u>Author conclusions:</u> 4 IV infusions of neridronate associated with clinically relevant and persistent benefits. Show use of bisphosphonates at appropriate doses an effective Rx choice for CRPS-1.			

Study	Methodology	Outcomes & results	Paper grading[9]		ACC reviewer comments & evidence level
Koivisto et al, 2014[8] BMC Musculosketal Disorders, 15:64 **Study design:** Single-centre, double-blinded, randomized, placebo-controlled trial **Research question:** To evaluate the efficacy of a single intravenous infusion of 5mg ZA vs intravenous placebo infusion in Lower Back Pain (LBP) and modic changes (MC) in MRI	<u>Population demographics</u> 98 participants with LBP and modal changes seen in MRI referred from a tertiary care unit (Oulu University Hospital). <u>Disorder / Inclusion criteria</u> Lower back pain symptoms for at least 3 months, pain intensity of at least 6 on the visual analog scale, and Oswestry Disability Index of at least 30%. MRI performed within 6 months prior to enrolment <u>Exclusion criteria</u> Renal impairment, hypocalcaemia, known hypersensitivity to ZA or other bisphosphonates, other red flags, nerve root entrapment, willingness for early retirement. Pre-menopausal women <u>Type of bisphosphonate:</u> Single intravenous infusion of 5 mg in 100ml solution ZA (n=20) or 100 ml Saline placebo over 15 minutes. Pain meds given before infusion (ibuprofen) for acute adverse reactions like headache or fever. Vit D given orally to prevent hypocalcaemia	<u>Demographics</u> 40 patients included (58 excluded for not meeting criteria). All 40 assessed at 1 month and 1 year post infusion <u>Main Findings</u> **Table 2 Low back symptoms and lumbar flexibility at baseline, one month and 12 months according to treatment group and between group comparisons of difference from baseline to one month and 12 months** Mean (SD) original values / Mean (SD) change / Unadjusted analyses / Adjusted analyses ZA n = 20 / Placebo n = 20 / ZA / Placebo / Difference (95% CI) / P / Difference (95% CI) / P* Intensity of LBP Baseline 6.6 (1.4) 6.8 (1.6) 1 month 4.3 (2.3) 5.8 (2.2) −2.2 (2.7) −0.9 (2.1) 1.3 (−0.2 to 2.8) 0.097 1.4 (0.01 to 2.9) 0.049 12 months 3.8 (2.5) 4.6 (2.9) −2.8 (2.9) −2.2 (2.5) 0.6 (−1.1 to 2.4) 0.474 0.7 (−1.0 to 2.4) 0.387 Intensity of leg pain[a] Baseline 3.0 (3.1) 2.9 (2.3) 1 month 2.0 (2.3) 3.0 (2.4) −0.6 (2.4) 0.1 (2.6) 0.8 (−0.9 to 2.4) 0.367 0.8 (−0.6 to 2.2) 0.237 12 months 2.1 (2.8) 2.7 (2.6) −0.9 (3.4) −0.3 (3.0) 0.6 (−1.5 to 2.7) 0.573 0.5 (−1.3 to 2.2) 0.573 Oswestry disability index, % Baseline 30 (11) 35 (10) 1 month 24 (10) 33 (13) −5.9 (11) −1.7 (9.7) 4.3 (−2.5 to 11) 0.212 6.0 (−0.6 to 13) 0.071 12 months 25 (13) 33 (15) −5.0 (15) −1.9 (12) 3.1 (−5.6 to 12) 0.475 5.1 (−3.4 to 14) 0.231 Main finding is that after 1 month there is a statistically significant decrease in LBP intensity with adjusted analyses only. However this is not present at 1 year.	Appropriate and focused question?	Y	Very small effect size that just reaches significance in positive statistics that are reported. Select cohort of participants – moderate to severe LBP with modal changes detected on MRI Patients reported a decrease in their use of NSAIDs, but no record or report was made about whether there were sudden changes to their pain regimen or if this was considered within the paper Well conducted double-blind RCT, however sample sizes are small and the statistics show a very small effect and only with adjusted measures. Interpreted as: the effect could easily diminish with larger sample sizes **Level of evidence: 1-**
			Subjects to treatment groups randomized?	Y	
			Adequate concealment method	Y	
			Subjects and investigator kept "blind"	Y	
			Treatment and control groups similar at the start of trial	Y	
			Only difference between groups is treatment under investigation	Y	
			Relevant outcomes are measured in a standard, valid and reliable way	Y	
			Percentage of individuals or clusters recruited to each treatment arm that dropped out of the study	0	
			All subjects analysed in groups to which they were randomly allocated (intention to treat analysis)	Y	
			If study performed across multiple sites, results are comparable for all sites	N	
			Are results of RCT directly applicable to BISph use for ACC clients?	CS	

[9] Y = yes, N = no, NA = not applicable, ? = can't say (information is missing or unclear)

	Outcome measures Performed at 1 month and 1 year after infusion. Primary measures: VAS Secondary: Leg pain intensity, ODI, Health related QOL scores with RAND-36, patient-reported sick leave, lumbar flexibility (fingers to floor and trunk side bending)	No other significant effects were found. Patients stated NSAID use had decreased at one year more often than those in placebo group Adverse effects Mild to moderate acute phase reactions previously described in literature **Table 4 Adverse events** **Adverse events** / **ZA n = 20** / **Placebo n = 20** Participants with at least one adverse event: 19 (95%) / 7 (35%) Acute phase reaction Flu like symptoms: 2 / 3 Fever: 19 / 1 Headache: 6 / 1 Myalgia: 15 / 4 Arthralgia: 6 / 0 Abnormal blood results Elevated CRP: 1 / 0 Serious adverse events Prevalence of at least one serious adverse event: 1 / 0 At least one non-elective hospital admission: 1 / 0 Death: 0 / 0 ZA = zoledronic acid. Author conclusions: Improvement in LBP was greater at 1 month after single ZA infusion compared to placebo. ZA should only be reserved for patients with severe disabling LBP with confirmed MC in MRI and when symptoms are not adequately controlled with pain medication and physiotherapy. Larger studies are required to prove the efficacy of ZA in patients with LBP due to MC			

<table>
<tr><th>Study</th><th>Methodology</th><th>Outcomes & results</th><th colspan="2">Paper grading[10]</th><th>ACC reviewer comments & evidence level</th></tr>
<tr>
<td rowspan="2">Laslett et al, 2012[9]

Annals of Rheumatic Diseases 71(8): 1322 - 1328

Study design:
Single-centre, double-blinded, randomized, placebo-controlled trial

Research question:
To compare the effect of a single infusion of zoledronic acid with placebo on knee pain and bone marrow lesions (BMLs)

Funding
Novatis Pharmaceuticals Australia;</td>
<td><u>Population demographics</u>
N = 59

<u>CRPS diagnosis</u>
Fulfilled
<u>Disorder / Inclusion criteria</u>
Knee OA defined by rheumatologist. Knee with most pain used as “study” knee
≥50 years with significant knee pain on most days (VAS≥40mm) and at least one BML detected on MRI
<u>Exclusion criteria</u>
Abnormal blood tests (eg, high levels of serum calcium), prior diagnosis of cancer, use of bisphosphonates, history of non-traumatic iritis/uveitis, severe knee OA (grade 3 on x-ray.
<u>Type of bisphosphonate:</u>
5mg ZA in 100mg of saline or placebo. Participants also advised to take paracetamol as prophylaxis for acute phase reactions</td>
<td><u>Demographics</u>
N = 59 (out of possible 88, 26 did not meet inclusion criteria, no BML in 9, other 4, declined to participate 1 and didn’t attend infusion apt 2)
Table 1 Characteristics of study participants at baseline, by treatment received
<table>
<tr><th></th><th>Zoledronic acid (n=31) mean (SD)</th><th>Placebo (n=28) mean (SD)</th></tr>
<tr><td>Age</td><td>64.2 (8.2)</td><td>60.4 (7.3)</td></tr>
<tr><td>Sex (% male)</td><td>61</td><td>54</td></tr>
<tr><td>BMI (kg/m²)</td><td>29.6 (4.4)</td><td>29.8 (5.8)</td></tr>
<tr><td>Baseline pain score (0–100)</td><td>49.5 (20.3)</td><td>55.1 (17.3)</td></tr>
<tr><td>Total bone marrow lesion area (mm²)</td><td>483.9 (410.2)</td><td>449.4 (339.3)</td></tr>
<tr><td>Medial tibial area</td><td>160.9 (250.4)</td><td>98.8 (126.6)</td></tr>
<tr><td>Medial femoral area</td><td>190.2 (249.6)</td><td>190.0 (265.1)</td></tr>
<tr><td>Lateral tibial area</td><td>66.3 (140.7)</td><td>54.4 (99.2)</td></tr>
<tr><td>Lateral femoral area</td><td>66.6 (164.3)</td><td>106.1 (157.2)</td></tr>
<tr><td>Radiographic OA (%)</td><td></td><td></td></tr>
<tr><td>OARSI grade 0</td><td>26</td><td>29</td></tr>
<tr><td>OARSI grade 1</td><td>23</td><td>25</td></tr>
<tr><td>OARSI grade 2</td><td>39</td><td>36</td></tr>
<tr><td>OARSI grade 3*</td><td>3</td><td>11</td></tr>
<tr><td>Medication use</td><td></td><td></td></tr>
<tr><td>Fish oil (%)</td><td>26</td><td>14</td></tr>
<tr><td>Glucosamine (%)</td><td>29</td><td>21</td></tr>
<tr><td>Paracetamol (%)</td><td>32</td><td>43</td></tr>
<tr><td>COX-2 inhibitors (any/none) (%)</td><td>35</td><td>46</td></tr>
<tr><td>Number of pain medications</td><td></td><td></td></tr>
<tr><td>0</td><td>26</td><td>21</td></tr>
<tr><td>1</td><td>35</td><td>43</td></tr>
<tr><td>2</td><td>32</td><td>25</td></tr>
<tr><td>3</td><td>7</td><td>11</td></tr>
<tr><td>Creatinine</td><td>71.6 (11.3)</td><td>69.2 (13.9)</td></tr>
<tr><td>eGFR</td><td>83.2 (7.7)</td><td>83.7 (8.6)</td></tr>
</table>
*OARSI grade 3 features are osteophytes, as participants with grade 3 joint space narrowing were excluded.
BMI, body mass index; COX-2, cyclooxygenase-2; eGFR, estimated glomerular filtration rate; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International.

<u>Adverse effects</u>
Occurred more frequently in the ZA group. Most significant effect was cold or flu</td>
<td>Appropriate and focused question?</td><td>Y</td>
<td rowspan="2">Good quality RCT that shows some decrease in pain at 6 months only that reversed back to no difference at 12 months in VAS scores in patients with Knee OA. Small improvement in bone marrow lesion area.

Larger and longer studies needed to assess effect

No reason for drop-outs given

Well conducted comprehensive RCT, not directly related to IPM for CRPS but shows short term effects of ZA infusion.

Level of evidence: 1+</td>
</tr>
<tr>
<td>Subjects to treatment groups randomized?
Adequate concealment method
Subjects and investigator kept “blind”
Treatment and control groups similar at the start of trial
Only difference between groups is treatment under investigation
Relevant outcomes are measured in a standard, valid and reliable way
Percentage of individuals or clusters recruited to each treatment arm that dropped out of the study
All subjects analysed in groups to which they were randomly allocated (intention to treat analysis)
If study performed across multiple sites, results are comparable for all sites
Are results of RCT directly applicable to BISph use for ACC clients?</td>
<td>Y
Y
Y
Y
Y
13.5
Y
NA
CS</td>
</tr>
</table>

[10] Y = yes, N = no, NA = not applicable, ? = can’t say (information is missing or unclear)

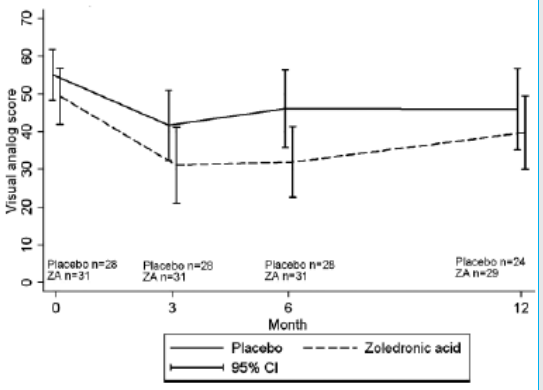
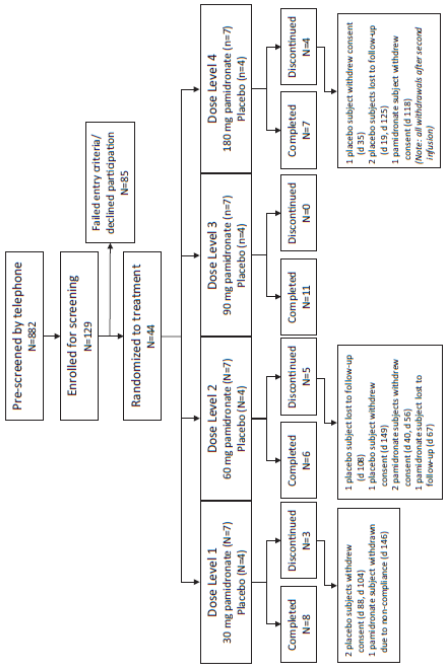
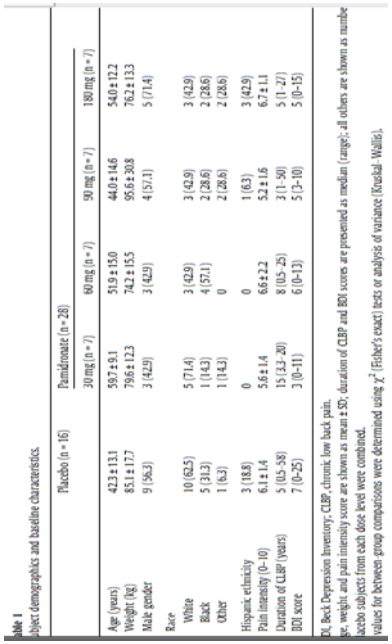
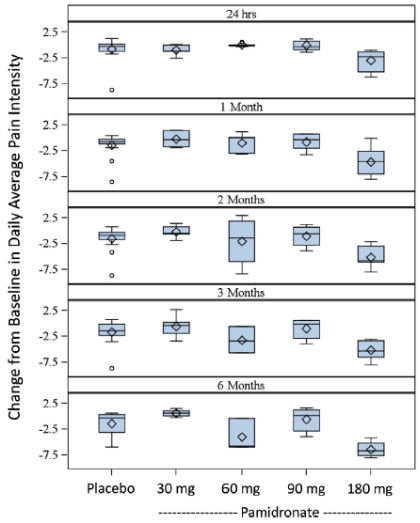
Australian government, National Health and Medical Research Council; and Osteoporosis Australia.	<u>Outcome measures</u> Primary outcomes: Pain intensity (VAS), max area of BML Secondary outcomes: pain intensity at 2 and 12 months, knee pain and symptoms at 3, 6, 12 months (using knee injury and osteoarthritis outcome score: KOOS questionnaire), Other medications allowed but kept constant throughout the trial period, records were obtained at baseline, 3, 6, and 12 months	symptoms **Table 5** Adverse events |	Zoledronic acid (n=31) n (%)	Placebo (n=28) n (%)	p Value | |---|---|---|---| | Adverse events | | | | | Participants with at least one adverse event | 31 (100%) | 19 (68%) | 0.001 | | Number of adverse events | 42 | 25 | 0.10 | | Acute phase reaction | 28 (90%) | 12 (43%) | 0.001 | | Cold or 'flu' symptoms | 22 | 7 | | | Uveitis | 2 | 0 | | | Increased knee pain | 3 | 0 | | | Abnormal blood results* | 10 (32%) | 12 (43%) | 0.40 | | Low creatinine | 4 | 3 | | | Low eGFR | 8 | 7 | | | Low corrected calcium | 3 | 2 | | | Knee replacements | 2 (6%) | 2 (7%) | 0.80 | | Elective surgery (excluding knee replacements) | 2 (6%) | 1 (4%) | 0.40 | | Serious adverse events | | | | | Prevalence of at least one serious adverse event | 6 (19%) | 1 (4%) | 0.11 | | Number of serious adverse events | 8 | 2 | 0.10 | | Cancer | 1 (3%) | 1 (4%) | 0.94 | | At least one non-elective hospital admission† | 6 (19%) | 1 (4%) | 0.09 | | Death | 0 (0%) | 0 (0%) | - | *Results of blood tests pooled for 3 and 6 month tests. †Non-elective admissions included removal of lymph node (in a patient with lymphoma), insertion of heart stent, heart valve repair, colonoscopy and cystoscopy (two operations in a patient with bladder cancer), knee pain, fractured pelvis and fractured elbow. eGFR, estimated glomerular filtration rate. <u>Main Findings</u>  **Figure 2** Pain scores (visual analogue scores) over the study time frame using unadjusted data and 95% CI of the point estimates. ZA, zoledronic acid.			

		 Table 2 Change in pain and knee symptoms between treatment groups (per protocol analysis) Baseline to 3 months: β Coefficient (95% CI) n=59 — p Value Baseline to 6 months: β Coefficient (95% CI) n=59 — p Value Baseline to 12 months: β Coefficient (95% CI) n=59* — p Value Pain score (visual analogue scale): −6.5 (−20.8 to 7.9) 0.37; −14.5 (−28.1 to −0.9) 0.04; −6.8 (−21.9 to 8.4) 0.24 Knee injury and osteoarthritis outcome score Pain scale: 2.6 (−8.6 to 13.7) 0.65; 6.2 (−2.5 to 14.9) 0.16; 3.2 (−8.3 to 14.7) 0.58 Symptom scale: 5.1 (−3.4 to 13.6) 0.24; 3.3 (−6.3 to 12.9) 0.50; 7.0 (−4.5 to 18.5) 0.23 Visual analogue score 0–100 where 0=no pain; 100=extreme pain. Negative change indicates improvement. Knee injury and osteoarthritis outcome score pain and symptom scales; 100=no problems; 0=extreme problems. Positive change indicates improvement. Adjusted for baseline medication use, age, sex and baseline pain score. *n=53 original data, n=5 imputed using the MICE system of chained equations. **Table 3** Change in bone marrow lesion size between treatment groups (per protocol analysis) Baseline to 6 months: β Coefficient (95% CI) n=59 — p Value Baseline to 12 months: β Coefficient (95% CI) n=59* — p Value Total area (mm²): −175.7 (−327.2 to −24.3) 0.024; −146.5 (−307.5 to +14.5) 0.07 Ordinal scale: −0.63 (−1.28 to +0.01) 0.05; −0.7 (−1.6 to 0.1) 0.104 Adjusted for baseline medication use, age, sex and baseline pain score. The ordinal scale measures the extent of bone size involved in the lesion. *n=51 original data, n=8 using imputed data. <u>Author conclusions:</u> ZA reduces knee pain and BML size and increases the proportion that improves over 6 months. Treatment of OA may benefit from a lesion specific therapeutic approach			

Study	Methodology	Outcomes & results	Paper grading[11]		ACC reviewer comments & evidence level
Pappagallo et al, 2014 [10] Pain, 155 (1), 108 – 117 **Study design** Randomised, double-blind, placebo-controlled, escalating-dose pilot study **Research question:** To assess the safety and efficacy of i.v. pamidronate in patients with centralised lower back pain and MRI imaging evidence of degenerative disk discase or spondylotic disease of the spine **Funding/Conflict of interest** Pappagallo has a patent for treating	**Pilot study:** 11 subjects enrolled into each arm (n = 44) that had either a placebo or dose of bisphosphonate administered.  Inclusion criteria At least 21 years old, had axial back pain persisting for at least 3 months. MRI evidence of disk degeneration and/or vertebral changes consistent with degenerative disk disease or spondylotic disease of lumbar spine	Demographics Largely the same across the dose concentration groups, only statistical difference is age (p=0.01)  Table 1 Subject demographics and baseline characteristics. Placebo (n = 16) Pamidronate (n = 28) 30 mg (n = 7) 60 mg (n = 7) 90 mg (n = 7) 180 mg (n = 7) Age (years) 42.3 ± 13.1 59.7 ± 9.1 51.9 ± 15.0 44.0 ± 14.6 54.0 ± 12.2 Weight (kg) 85.1 ± 17.7 79.6 ± 12.3 74.2 ± 15.5 95.6 ± 30.8 76.2 ± 13.3 Male gender 9 (56.3) 3 (42.9) 3 (42.9) 4 (57.1) 5 (71.4) Race White 10 (62.5) 5 (71.4) 3 (42.9) 3 (42.9) 3 (42.9) Black 5 (31.3) 1 (14.3) 4 (57.1) 2 (28.6) 2 (28.6) Other 1 (6.3) 1 (14.3) 0 2 (28.6) 2 (28.6) Hispanic ethnicity 3 (18.8) 0 0 1 (6.3) 3 (42.9) Pain intensity (0–10) 6.1 ± 1.4 5.6 ± 1.4 6.6 ± 2.2 5.2 ± 1.6 6.7 ± 1.1 Duration of CLBP (years) 5 (0.5–58) 15 (3.3–20) 8 (0.5–25) 3 (1–50) 5 (1–27) BDI score 7 (0–25) 3 (0–11) 6 (0–13) 5 (3–10) 5 (0–15) CLBP, chronic low back pain. Age, weight, and pain intensity score are shown as mean ± SD; duration of CLBP and BDI scores are presented as median (range); all others are shown as number of placebo subjects from each dose level were combined. Values for between group comparisons were determined using χ^2 (Fisher's exact) tests or analysis of variance (Kruskal–Wallis). Change in average pain scores Decreases seen at all doses, however 180mg was significantly different compared to other groups at 1 – 6 months post infusion	Appropriate and focused question?	Y	**Pilot study of 4 different doses of iv pamidronate in CLBP.** **Study states molecular mechanisms of pamidronate's analgesic effects are not fully understood** **Well conducted and thorough pilot RCT that shows decreases in pain scores with the cumulative (2 x 90mg) dose of IV pamidronate.** **High drop-out of participants and low numbers of participants due to it being a pilot study. Also study was highly restricted with its inclusion/exclusion criteria which may make it less relevant for ACC clients as results cannot be generalised.** **Level of evidence: 1-**
			Subjects to treatment groups randomized?	Y	
			Adequate concealment method	Y	
			Subjects and investigator kept "blind"	Y	
			Treatment and control groups similar at the start of trial	Y	
			Only difference between groups is treatment under investigation	Y	
			Relevant outcomes are measured in a standard, valid and reliable way	T	
			Percentage of individuals or clusters recruited to each treatment arm that dropped out of the study	27.3	
			All subjects analysed in groups to which they were randomly allocated (intention to treat analysis)	T	
			If study performed across multiple sites, results are comparable for all sites	NA	
			Are results of RCT directly applicable to BISph use for ACC clients?	CS	

[11] Y = yes, N = no, NA = not applicable, ? = can't say (information is missing or unclear)

chronic spinal mechanical pain with IV admin of biphsphonate, and he and Moberly re employees of Grunethal Funded by: US NIH grant and grant from National Centre for Research resources	average pain of >4 on numeric rating Exclusion criteria If had prior back surgery, compression vertebral fracture, cancer as cause of pain, MRI evidence of disk herniation or other extraspinal structural pathology, defect or fracture of pars-interarticularis, radiculopathic or neuropathic leg pain, back pain with neurological deficits, hypocalcemia, renal issues, allergy to bisphosphonates, pregnant, weight <45kg, abused alcohol, had workers' compensation, were blind deaf, mute or had physical or mental disability, and had a back depression inventory score of <26, dental procedures, cancer treatments, steroid injections or anticipated to need injections. Bisphosphonate agent 30, 60 or 90mg of disodium pamidronate in 250ml of saline over 4 hours IV. 180mg dose delivered over two 90mg doses with 4 week period between, effects measures started from second dose Comparisons Pain measures from electronic diaries at 24 hrs, 1,2,3 and 6 months. Physical examinations every month, blood tests at 2 weeks after infusion, then every month Adverse events Subjects self-reported using an electronic diary, and coordinator made phone-calls at 1,2,and 3 days after infusion	 . 2. Box and whisker plot of change from baseline in daily average pain score. bottom and top edges of each box represent the 25th and 75th percentiles terquartile range [IQR]). Within each box, the median (50th percentile) is played as a line and the mean as a diamond. Whiskers extending from each box icate the range of values outside the IQR. Points at a distance of more than 1.5 × IQR from the box are considered outliers. Oswestry disability index and EuroQol scores showed no significant difference among treatment groups at 3 and 6 months. Opioid pain medications were used less frequently by subjects classed as responders (average daily pain score decreased by at least 30%, or 2 points n = 20). At 6 months proportion of subjects using nonopioid analgesics was lower for responders vs non-responders Imaging results No significant correlation between bone mineral density and analgesic response to pamidronate treatment Adverse effects Acute phase responses seen in pamidronate Rx groups mainly in first			

		week of treatment. Headache and flu-like symptoms seen. No clinically meaningful changes in ECG or laboratory findings in Rx group. <u>Author conclusions:</u> IV pamidronate administered as two 90mg infusions produced a sustained and clinically significant decrease in pain intensity in subjects with CLBP and MRI evidence of degenerative disk disease or spondylotic disease of the spine. Pilot is for a limited number of highly selected subjects and results cannot be generalised. Further studies needed to confirm findings and assess overall risks and benefits of this population before any medical recommendation can be made for use of pamidronate in therapy of CLBP			

7.4 Appendix 4: External peer-review request: Comparison of Varenna et al, 2013 against Robinson et al, 2014

7.4.1 Overview of quality appraisal for Varenna et al (2013) and Robinson et al, (2004)

The table below shows that the main difference between these studies was the bisphosphonate that was used (pamidronate and neridronate). Outcomes were measured using similar scoring systems (VAS, SF-36), and there some similarities of the time points they were measured at (baseline, and around 1 month). Differences that should be noted are: Robinson (2004) measured outcomes at a defined longer period than Varenna, and that Varenna were able to include a much larger cohort of participants. Neither study examined results for upper and lower limb separately,

Table 9. Overview of methods for Varenna et al, 2013; and Robinson et al, 2004

Author	Study design	Bisphosphonate infusion details	CRPS Details	Outcomes	Level of evidence
Robinson et al, (2004)	Single-centre, double-blinded, randomised, placebo-controlled trial	Single IV infusion of pamidronate or placebo: Dose: 60mg Placebo: Saline infusion	Diagnosis: International Study for the Study of Pain (ISAP) criteria Cohort Lower limb = 13 Upper limb = 14 Disease duration: 2 months – 6 years Treatment group: n = 14 Placebo: n = 13	Measured at baseline then 1 and 3 months Visual analogue scale (VAS) scores Global assessment of disease severity SF-36 quality of life health survey	1 -
Varenna et al, (2013)	Prospective double-blinded, randomised, placebo-controlled study	IV infusion of Neridronate (structurally similar to pamidronate) Dose: 100mg, four times over 10 days (given every 3rd day) Placebo: 500mL saline	Diagnosis: Budapest criteria At least 18 years old, CRPS-1 of hands or feet for no longer than 4 months, spontaneous pain intensity of 50 – 100mg on VAS, 3 phase bone scintigraphy obtained Cohort Treatment, n = 41 Placebo, n = 41 Lower limb treatment, n = 33 Lower limb placebo, n = 29 Upper limb treatment, n = 8 Upper limb placebo, n = 12	Outcomes measured at : Day 1 (first infusion), Day 10 (last infusion, at 20 days, then 40 days. Long-term follow-up (several months, number not stated) VAS scores SF-36 Scores (included scores for physical functioning, social functioning, limitations to physical or emotional problems, general health) After initial study an open extension was conducted where participants in the placebo arm were given the treatment open label. No serious drug effects	1+

7.4.2 Overview of results of Varenna et al (2013) and Robinson et al (2004)

Both of these studies showed decreases in VAS scores and increases in SF-36 scores after bisphosphonate infusion. Also both had similar adverse effects that resolved without any further interventions.

Table 10. Main results of Varenna et al (2013) and Robinson et al (2004)

Study	Main finding
Robinson et al, 2004 (RCT)	**VAS Scale** - No difference between control and treatment: before pamidronate given, at 1 month post pamidronate infusion - Significant difference (P = 0.026) seen between control group and treatment group at 3 months, with treatment group having a lower median VAS score - The biggest change in VAS score in the treatment group was also seen at 0 – 3 months (P = 0.048) - The interquartile range between the control and treatment groups are similar **SF-36** - SF-36 was documented at baseline, 1 and 3 months - Participants in the treatment group had higher scores than the control group (P = 0.047) at 3 months (the higher the score indicates less disability) **Adverse / side effects** - Influenza type symptoms (n = 5 in treatment group, n = 2 in control) - Mild infusion site reactions (erythema, discomfort) n = 2 in treatment group - All symptoms resolved in 6 – 48 hours **Other pain regimens** - Background analgesia continued throughout the study, and doses were held stable throughout the treatment period - Analgesia included: paracetamol (4g/day), codeine phosphate (120 – 180mg/day as monotherapy or with paracetamol) and paracetamol (325mg) / dextropropoxyphene (50mg) combination (up to 8 per day)
Varenna et al, 2013 (RCT)	**VAS Scale** - Neridronate participants had a statistically significant lower VAS mean at 20 days compared to placebo which increased at 40 days **SF-36** - Statisticlally significant differences in: Physical function, role limitations due to physical health, emotional well-being, social functioning, pain, physical component scores. - Highest scores reported for physical functioning, role limitations due to physical health and emotional well being **Adverse / side effects** - N = 21 neridronate, 12 = placebo complained of at least of one effect. - Polyarthalgia: 12 for neridronate, 5 placebo - Fever: 9 neridronate, 1 placebo - Effects disappeared after 3 days, no serious drug-related effects reported during study **Other pain regimens** - It was not stated that pain regimens were restricted in this study - The uses of NSAIDSs or paracetamol were used as a measure of the effects of neridronate on pain - All patients receiving treatment, and 45% of placebo discontinued symptomatic drugs in 2 weeks of receiving infusion