General Practitioner, Dr A

Medical Centre

A Report by the

Deputy Health and Disability Commissioner

(Case 17HDC00010)

Health and Disability Commissioner
Te Toihau Hauora, Hauātanga

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Executive summary

1. Mrs B had a complicated medical history, including chronic renal disease, and was receiving diuretics. Mrs B had been identified by the Pain Clinic at the public hospital as a good candidate for pamidronate[1] trials to treat sciatica and spinal stenosis symptoms. However, Mrs B did not start on the trial immediately.

2. The public hospital had blood test results available which indicated deterioration in Mrs B's renal function over a twelve month period up and including Month10[2] 2016. These were accessible by Mrs B's general practitioner, Dr A.

3. On 16 Month10, Dr A offered Mrs B a zoledronic acid (Aclasta)[3] infusion for pain relief, believing zoledronic acid and pamidronate to be interchangeable.

4. Mrs B was provided with an information sheet, signed a consent form, and received the infusion, prescribed and ordered by Dr A.

5. At the time of these events, the medical centre did not have in place a zoledronic acid infusion protocol or a pre-infusion checklist.

6. In the days following the infusion, Mrs B became increasingly unwell. She was admitted to hospital on 27 Month10 and blood tests showed acute chronic renal failure. Sadly, Mrs B died that day.

7. The medsafe datasheet for zoledronic acid states that the use of zoledronic acid in patients with severe renal impairment is contraindicated owing to the increased risk of renal failure in this population. Calculation of creatinine clearance levels should be undertaken to check the risk of renal adverse reactions. Concomitant diuretic therapy is also a risk factor for renal failure.

Findings

8. The Deputy Commissioner was critical that Dr A offered Mrs B zoledronic acid in place of pamidronate without realising that they were not interchangeable, and had different clinical indications and pharmacokinetic profiles.

9. Dr A did not assess Mrs B's condition adequately before prescribing and ordering the administration of zoledronic acid, and did not ensure that he was familiar with the contraindications of the medication before prescribing it. The Deputy Commissioner found that Dr A failed to provide services to Mrs B with reasonable care and skill and, accordingly, breached Right 4(1) of the Code.

10. The Deputy Commissioner considered that in prescribing and ordering the administration of zoledronic acid to Mrs B, Dr A was acting within the medical centre's authority. Therefore, the medical centre was found vicariously liable for Dr A's breach of Right 4(1) of the Code.

[1] Pamidronate is administered in the treatment of some bone diseases and bone pain.
[2] Relevant months are referred to as Months 1-10.
[3] Zoledronic acid is used in primary care to treat osteoporosis. It is also called zoledronate. Aclasta is a brand (trade) name for zoledronic acid.

11. **Recommendations**
The Deputy Commissioner recommended that the medical centre undertake an audit of all patients who have received zoledronic acid infusions in 2018 to confirm renal function investigations are being considered prior to a zoledronic acid infusion being given, that the Medical Council of New Zealand consider whether a review of Dr A's competence is warranted, and that Dr A provide a written apology to the family.

Complaint and investigation

12. The Commissioner received a complaint from Dr C about the services provided to Mrs B by Dr A at the medical centre.[4] The following issues were identified for investigation:

- *Whether the medical centre provided Mrs B with an appropriate standard of care in Month10 2016.*
- *Whether Dr A provided Mrs B with an appropriate standard of care in Month10 2016.*

13. This report is the opinion of Kevin Allan, Deputy Commissioner, and is made in accordance with the power delegated to him by the Commissioner.

14. The parties directly involved in the investigation were:

Dr A	General practitioner (GP)
Medical centre	Provider
Dr C	Complainant
Consumer's husband/executor of the estate	
Consumer's daughter	

15. Expert advice was obtained from in-house vocationally registered general practitioner Dr David Maplesden (**Appendix A**).

Information gathered during investigation

Background

16. Mrs B was enrolled with the medical centre in 1974 and Dr A had been her principal general practitioner since 1990.

17. Mrs B had a complicated medical history, and by 2016 she suffered from type two diabetes, cardiac disease, chronic renal disease, peripheral vascular disease,[5] peripheral neuropathy,[6] and obesity. Mrs B was also receiving diuretics.

[4] Dr A is a shareholder of the medical centre.
[5] Vascular disease affecting blood vessels outside of the heart and especially those vessels supplying the extremities.

18. In Month1, Mrs B was referred to the Pain Clinic at a public hospital by Dr A for consideration of epidural steroids for her sciatica and spinal stenosis symptoms. The referral was not accepted immediately. However, on 12 Month5 an epidural[7] steroid injection was given in an effort to alleviate Mrs B's lumbar pain. Later, in Month7, a consultant anaesthetist/pain specialist from the Pain Clinic then identified Mrs B as a good candidate for pamidronate trials. However, Mrs B did not start on the trial immediately.

Relevant monitoring

19. On 24 Month3, Mrs B's height and weight measurements were recorded in her clinical records at the medical centre by a practice nurse.

20. Renal function blood tests were taken and monitored by the public hospital for the 12 months leading up to (and including) Month10. These results were available to Dr A and were noted in Mrs B's medical records on 10 Month3. The trends in these results included changes in her creatinine[8] levels and eGFR[9] and indicated deterioration in her renal function.

Zoledronic acid (Aclasta) infusion

21. On 16 Month10, Mrs B attended the medical centre. Dr A told HDC:

> "[Mrs B] attended with her husband in a miserable state with chronic leg pain, leg swelling with early ulceration. They recounted [the consultant anaesthetist/pain specialist's] suggestion of a Pamidronate Infusion. [Mrs B] was keen to try anything to give her some relief. My initial plan was to ring … the Pain Clinic to expedite this referral, however realising that it was […] it appeared unlikely that anything was going to happen quickly."

22. Dr A offered Mrs B a zoledronic acid (Aclasta) infusion. Dr A told HDC that many of his patients have received zoledronic acid infusions for osteoporosis and have reported an improvement in chronic back pain symptoms similar to the intended outcome of the pamidronate trials.

23. Dr A told HDC that he believed zoledronic acid and pamidronate to be interchangeable. He has since accepted that this is incorrect.

24. On 19 Month10, Mrs B signed a consent form that read: "I am aware that today I will be receiving a zoledronic acid (Aclasta) Infusion. I have had explained to me the purpose, procedure and possible adverse effects. I agree to this procedure taking place."

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[6] A disease or degenerative state of the peripheral nerves in which motor, sensory, or vasomotor nerve fibers may be affected and which is marked by muscle weakness and atrophy, pain, and numbness.

[7] An injection of a local anaesthetic into the space outside the dura mater of the spinal cord in the lower back region to produce loss of sensation especially in the abdomen or pelvic region.

[8] A normal waste product from the breakdown of protein in muscles which is removed from the body by the kidneys. If the kidneys are not working well there is more creatinine in the blood. Reference range is 45–90µmol/L.

[9] A calculation to estimate the glomerular filtration rate. An eGFR gives an estimate of the percentage of normal kidney function. Reference range is >60ml/min/1.73m^2.

25. Mrs B was provided with an information sheet which stated that adequate fluid intake should be maintained by drinking extra water. It also stated that a dosage of calcium and/or vitamin D supplements should be taken, and that flu-like symptoms may occur within three days of the infusion. Listed side effects included fever, chills, pain in the muscles/joints/bones, nausea, fatigue, and headache. In the event that any of the symptoms were experienced, the sheet recommended taking paracetamol. If any side effects were severe, urgent referral to a GP was recommended.

26. An intravenous cannula[10] was then inserted and the zoledronic acid infusion commenced by Dr A.

27. At the time of these events, the medical centre did not have in place a zoledronic acid infusion protocol or a pre-infusion checklist.

28. The Medical Clinic's notes for these two visits state:

> "Visit date: 16 [Month10], 9:00
> Examination notes: Pain specialist recommended Aclasta but has not organised to see Monday to have Aclasta here.
>
> Visit date: 19 [Month10], 8:45
> Aclasta infusion cannula inserted and infusion commenced by [Dr A] this is a one off Aclasta. Pain team had advised she was a good candidate and [Dr A] booked app. No further needed.
>
> Visit date: 19 [Month10], 9:03
> Examination notes: Scanned Aclasta Infusion Consent."

29. In the days following the infusion, Mrs B became increasingly unwell. She was admitted to the public hospital on 27 Month10, and it was noted that she had experienced malaise, a loss of appetite, and anuria.[11] Mrs B was observed as being confused, acidotic,[12] and hypertensive, and blood tests showed acute on chronic renal failure and hyperkalaemia.[13] A palliative care approach was adopted, and Mrs B died that same day.

Use of zoledronic acid

30. The Medsafe datasheet for Aclasta[14] (zoledronic acid) states that the use of zoledronic acid in patients with severe renal impairment (creatinine clearance[15] <35mL/min) is contraindicated owing to the increased risk of renal failure in this population. It also states that renal impairment has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal impairment or other risk factors including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration occurring after zoledronic acid administration.

[10] A tube placed into a vein to allow delivery or removal of fluid.
[11] The absence or defective excretion of urine.
[12] A pathological state characterised by an increase in the concentration of hydrogen ions in the arterial blood above the normal, or pH less than 7.4.
[13] The presence of an abnormally high concentration of potassium in the blood.
[14] http://www.medsafe.govt.nz/profs/datasheet/a/Aclastainf.pdf
[15] Creatinine clearance is the amount of blood the kidneys can make creatinine free each minute. It is used to approximate the glomerular filtration rate and is an indication of kidney function.

31. The datasheet states that creatinine clearance levels should be calculated before each dose (eg, Cockcroft-Gault formula) to minimise the risk of renal adverse reactions. This can be done using an online tool that takes into account the sex, age, weight, and creatinine level of a patient.

Dr C

32. Dr C, a registrar from the public hospital, lodged a complaint with HDC raising concerns about Mrs B's care. Dr C stated:

> "[Mrs B] was given a bisphosphonate[16] infusion by her GP less than a week prior [to her death]. Her renal function was documented in [Month9] as being significantly impaired with an eGFR of 19 and a creatinine of 289. Bisphosphonate infusions are contraindicated with an eGFR of less than 35 due to the risk of renal impairment …"

Dr A's explanation

33. Dr A told HDC:

> "I have been to several Educational Sessions regarding this [zoledronic acid] Infusion. My understanding was that there was a relative precaution regarding Renal Impairment which was accounted for by reducing the rate of the Infusion [and] extending the time of administration. It is my regret that I had not at any stage registered a contra-indication in degrees of severe Renal Impairment."

34. Dr A noted the following discrepancies between the manufacturing recommendations and the local laboratory reports:

> "… Manufacturers Recommendations for Kidney Function are based on 'Creatinine Clearance' but our local Laboratory only reports 'estimated Glomerular Filtration rate or GFR.' These two calculations are not the same thing. [Mrs B's] renal function was very poor with a GFR of 19mlpm. Using an online Cockcroft Gault calculator, this translates to a Creatinine Clearance [rate] of 31mlpm. The manufacturer of [zoledronic acid] indicates a contra-indication for its use with a creatinine clearance below 30. However the Aclasta Brand that we use advises not administering with a Creatinine Clearance of below 35."

35. Dr A told HDC that since receiving this complaint, the medical centre has undertaken calculations to ensure that other patients have not been affected. Dr A stated that he accepts that there was no robust protocol and checklist ensuring that all appropriate pre-infusion testing and patient advice was given; that there is no clinical documentation to show what advice was provided to Mrs B in relation to hydration cautions or other safety-netting advice; and that he ordered the administration of the zoledronic acid infusion to Mrs B, whose renal function was severely impaired.

[16] A group of medicines used to treat bone disease such as osteoporosis and Paget's disease. Pamidronate and zoledronic acid are examples of injectable bisphosphonates.

Changes made to practice at the medical centre

36. In January 2017, the medical centre updated its information sheet about zoledronic acid infusions to include information about the purpose of the infusion, administration of the infusion, and potential side effects.

37. Also in January 2017 the medical centre introduced an Aclasta acid infusion checklist, which includes fields to insert eGFR level, creatinine level, patient weight, patient height, and creatinine clearance. Additional fields include "allergies identified", "oral bisphosphonate stopped", "diuretics stopped", "information sheet given/read", and "2 extra glasses of water prior to infusion, vitamin D prescribed by GP, calci tabs prescribed by GP". An additional field prompts the person administering the infusion to advise the patient to maintain adequate fluid intake after the infusion.

Further information – the family

38. Mrs B's family provided feedback during the course of the investigation and in response to the provisional decision. The family emphasised that they are appreciative of the care provided by Dr A to Mrs B, and his efforts to alleviate her suffering.

39. Dr A and the medical centre were given an opportunity to comment on the provisional opinion. Dr A responded on behalf of himself and the medical centre, and advised that he accepts the provisional findings and agrees to undertake the recommendations made.

Relevant standards

40. The Medical Council of New Zealand statement *Good prescribing practice* provides:[17]

> "You should only prescribe medicines or treatment when you have adequately assessed the patient's condition, and/or have adequate knowledge of the patient's condition and are therefore satisfied that the medicines or treatment are in the patient's best interests …
>
> Be familiar with the indications, adverse effects, contraindications, major drug interactions, appropriate dosages, monitoring requirements, effectiveness and cost-effectiveness of the medicines that you prescribe …
>
> Prescribe in accordance with accepted practice and any relevant best practice guidelines …
>
> Keep a clear, accurate and timely patient record containing all relevant clinical findings; decisions made; adverse drug reactions (date, name of medicine and description of reaction); information given to the patient about the medicines and any other treatment prescribed."

[17] https://www.mcnz.org.nz/assets/News-and-Publications/Statements/Good-prescribing-practice.pdf

Opinion: Dr A — breach

41. In Month7, Mrs B was identified as a candidate for a pamidronate trial by the Pain Clinic at the public hospital. On 16 Month10, Mrs B's trial had not yet begun and she presented to the medical centre in pain. Dr A told HDC that Mrs B told him about the suggestion of a pamidronate infusion and he offered to give her a zoledronic acid (Aclasta) infusion. Dr A told HDC that many of his patients have received zoledronic acid infusions for osteoporosis and have reported an improvement in chronic back pain symptoms. Dr A said that he believed zoledronic acid and pamidronate to be interchangeable.

42. Mrs B signed a consent form and received a zoledronic acid infusion on 19 Month10, which was prescribed by Dr A.

Offer of zoledronic acid in place of pamidronate — adverse comment

43. My in-house clinical advisor, GP Dr David Maplesden, has advised HDC that pamidronate and zoledronic acid infusions are not interchangeable. Dr Maplesden advised:

> "[Pamidronate] has a different clinical indication and a different pharmacokinetic profile to [zoledronic acid] … In particular, the manufacturers of pamidronate note: pharmacokinetic studies indicate that no dose adjustment is necessary in patients with any degree of renal impairment. However, until further experience is gained a maximum infusion rate of 20 mg/h is recommended in renally impaired patients."

44. Dr Maplesden noted that Mrs B's renal function was severely impaired.

45. I accept Dr Maplesden's advice that these medications are not interchangeable, and Dr A has since accepted that his understanding at the time was incorrect. I am concerned that Dr A offered Mrs B zoledronic acid in place of pamidronate without realising that they were not interchangeable, and had different clinical indications and pharmacokinetic profiles.

Contraindication — breach

46. Mrs B's most recent creatinine levels and eGFR results were documented in her medical record as 213µmol/L and 19mL/min respectively on 11 Month9. They had deteriorated over the past year. It is of note that Mrs B was also taking diuretics.

47. As stated above, the Medsafe datasheet for Aclasta states that the use of Aclasta in patients with severe renal impairment, namely a creatinine clearance <35mL/min, is contraindicated and that the creatinine clearance rate should be calculated before administration. It also notes that patients receiving diuretic therapy are at increased risk of renal impairment following administration of zoledronic acid.

48. When using a tool that adjusted for Mrs B's BMI, Dr Maplesden advised that the creatinine clearance calculated as 24.1mL/min. Dr Maplesden also advised that when he calculated Mrs B's creatinine clearance using a general calculation (not accounting for Mrs B's BMI) this (31mL/min) was also within the range for which use of Aclasta is contraindicated according to the New Zealand sources he consulted. I accept this advice.

49. Dr Maplesden further advised:

> "I am severely critical that [Dr A] chose to order the administration of [a zoledronic acid] infusion to a patient whose renal function was severely impaired either without

> calculating the patient's creatinine clearance, or if he did make such a calculation, he authorised the infusion when results would have indicated a contraindication to use of the drug. The clinical notes do not suggest there was any calculation of creatinine clearance prior to administration yet sequential blood results in the previous 12 months had shown progressive deterioration in renal function and the eGFR, at 19 mL/min, was certainly sufficiently concerning to warrant as accurate a determination as possible of creatinine clearance prior to authorizing the infusion. Furthermore, [Mrs B] was taking diuretics which increased her risk of acute renal impairment known to be associated with use of the drug."

50. As Dr Maplesden noted, there is no record in Mrs B's clinical notes of a creatinine clearance calculation taking place, and Dr A has also not told HDC that any such calculation was carried out. Further, since receiving this complaint, Dr A told HDC that the medical centre has undertaken calculations to ensure that other patients have not been affected. Having considered all of this information, I find that Dr A did not calculate the creatinine clearance rate before administering the Aclasta to Mrs B.

51. I note that Dr A has suggested that there was some difference between the manufacturer of zoledronic acid and the Aclasta brand regarding the creatinine clearance rate that is contraindicated. However, in order to establish whether there was a contraindication under any measure, a calculation would first have had to be done. I have found that it was not. In any event, the Medsafe datasheet states that the use of Aclasta (the product that Dr A was using) in patients with severe renal impairment, namely a creatinine clearance <35mL/min, is contraindicated. As above, Dr Maplesden has advised that both the rates he calculated using a tool adjusted for BMI and a general tool were below 35mL/min and were within the range for which use of Aclasta is contraindicated according to the New Zealand sources he consulted.

52. I accept Dr Maplesden's advice above, and am concerned that Dr A chose to prescribe and order the administration of zoledronic acid to Mrs B without first calculating her creatinine clearance, despite her clinical records showing a progressive deterioration in her renal function in the previous 12 months and the fact that she was taking diuretics. In this regard, I am also concerned that, as he has accepted, Dr A lacked awareness that severe renal impairment was contraindicated. I consider that Dr A failed to comply with the MCNZ *Good Prescribing Practice* statement in that he did not assess Mrs B's condition adequately before prescribing and ordering the administration of Aclasta, and did not ensure that he was familiar with the contraindications of the medication before prescribing it. For these reasons, I consider that Dr A failed to provide services to Mrs B with reasonable care and skill and, accordingly, breached Right 4(1) of the Code.

Opinion: Medical centre — breach

53. Section 72(2) of the Health and Disability Commissioner Act 1994 (the Act) states that an employing authority is vicariously liable for any acts or omissions of its agents unless they are done or omitted without that employing authority's express or implied authority.

54. Dr A has told HDC that he is a shareholder, director and, as a medical practitioner, a contractor to the medical centre. In his role as a contractor of the medical centre he was

authorised to act on behalf of the medical centre and was therefore an agent of the medical centre.

55. I consider that in prescribing and ordering the administration of zoledronic acid to Mrs B, Dr A was acting within the medical centre's authority. Therefore, the medical centre is vicariously liable for Dr A's breach of Right 4(1) of the Code.

56. I note that Dr Maplesden advised:

> "[The Medical Clinic's] previous documentation which did not include an infusion protocol or pre-infusion checklist, I would regard as being seriously deficient and departing from expected standards of care to at least a moderate degree."

57. However, following this event, the medical centre introduced a new protocol and checklist. Dr Maplesden reviewed this information and advised that the documentation meets the expected standard. I consider these changes to be both necessary and appropriate in the circumstances.

Recommendations

58. I recommend that Dr A provide a written apology to the family. The apology is to be sent to HDC within three weeks of the date of this report, for forwarding to the family.

59. I recommend that the Medical Council of New Zealand consider whether a review of Dr A's competence is warranted.

60. I recommend that the medical centre undertake an audit of all patients who have received zoledronic acid infusions in 2018, in order to confirm that eGFR levels are being identified and considered prior to a zoledronic acid infusion being given. The results of the audit should be provided to HDC within three months of the date of this decision along with an action plan to address any issues identified from the audit.

Follow-up actions

61. A copy of this report with details identifying the parties removed, except the expert who advised on this case, will be sent to the Medical Council of New Zealand, and it will be advised of Dr A's name in covering correspondence.

62. A copy of this report with details identifying the parties removed, except the expert who advised on this case, will be sent to the Royal New Zealand College of General Practitioners, the Health Quality & Safety Commission, and the New Zealand Pharmacovigilance Centre.

63. A copy of this report with details identifying the parties removed, except the expert who advised on this case, will be placed on the Health and Disability Commissioner website, www.hdc.org.nz, for educational purposes.

Appendix A: Independent in-house clinical advice to the Commissioner

The following expert advice was obtained from Dr David Maplesden:

"1. Thank you for providing this file for advice. To the best of my knowledge I have no conflict of interest in providing this advice. I have reviewed the available information: complaint from [registrar Dr C]; response from [Dr A] of [the medical centre]; clinical notes [the medical centre]; clinical notes [the public hospital]; selected Coronial correspondence.

2. [Dr C] has expressed concerns at the management of [Mrs B] (dec) by staff of [the medical centre]. [Mrs B] was admitted to [the public hospital] on 27 [Month10] several days after undergoing an infusion of Aclasta (zoledronic acid) at [the medical centre]. Following the infusion [Mrs B] had become increasingly unwell with malaise and loss of appetite, and she had anuria for three days prior to admission. She was noted to be confused, acidotic and hypotensive and blood tests showed acute on chronic renal failure and hyperkalaemia. Following discussion with family members a palliative approach was taken and [Mrs B] died about 12 hours following admission. [Dr C] is concerned that blood tests prior to the Aclasta infusion had shown [Mrs B's] renal function was significantly impaired, and Aclasta infusion is contraindicated in patients with creatinine clearance less than 35 ml/min. She states [Mrs B] was also taking diuretics and antihypertensive agents and had not been instructed to increase her fluid intake following the infusion. She is concerned that the [the medical centre] practices and procedures associated with Aclasta infusions may be unsafe.

3. [Public hospital] notes are consistent with the response. I note [Mrs B] was also found to have a Klebsiella urinary tract infection during the admission and that urosepsis can be associated with acute deterioration in renal function. [Mrs B's] death certificate identified immediate cause of death as *renal failure 3 days* with antecedent causes notes as *chronic renal failure, urosepsis, nephrotoxic medications 4 years.* Additional conditions present but not directly related to the cause of death were ischaemic heart disease, type 2 diabetes and COPD. There is an e-mail record between [Dr C] and the Coroner's office in which concern is expressed at [Mrs B's] preceding Aclasta infusion in light of her impaired renal function.

4. [Medical centre] response ([Dr A])

(i) [Mrs B] had been a patient at [the medical centre] since 1974 and enrolled with [Dr A] since 1990. [Dr A] states: *Her principal medical problem for many years was Type 2 Diabetes but as the years progressed she developed numerous complications of this with Cardiac disease, Chronic Renal disease, Peripheral Vascular disease, Peripheral Neuropathy. She also became increasingly obese finally weighing 94kg with a height of only 144cm. Subsequent to this she developed symptoms of Spinal Stenosis which was not operable because of her other co-morbidities.*

(ii) [Mrs B] was on multiple medications at the time of her death including Cartia, Betaloc, Frusemide, Losec, gabapentin, isosorbide mononitrate, enalapril, nifedipine, simvastatin, Paracodeine, metformin, perhexiline, allopurinol and spironolactone.

(iii) [Mrs B] had been referred for pain specialist input in [Month1] in relation to her spinal stenosis and sciatica. And epidural steroid injection in [Month5] had given only moderate relief and following a pain service consultation in [Month7] [Mrs B] was placed on the waiting list for a trial pamidronate infusion.

(iv) [Dr A] states: *On 16th [Month10] [Mrs B] attended with her husband in a miserable state with chronic leg pain, leg swelling with early ulceration. They recounted* [the consultant anaesthetist/pain specialist's] *suggestion of a Pamidronate Infusion. [Mrs B] was keen to try anything to give her some relief. My initial plan was to ring …the Pain Clinic to expedite this referral, however […] it appeared unlikely that anything was going to happen quickly. In this Practice we have been doing regular Zolendronate (Aclasta) Infusions for the treatment of Osteoporosis. Many of the recipients have spontaneously reported an improvement in their Chronic Back Pain Symptoms, similar to the intended outcome of the Pamidronate Trial. With this in mind, I suggested to [Mrs B] that we could do a Zolendronate Infusion for her as we did have some surplus infusions in stock. This infusion was performed on 19th [Month10]*.

(v) [Dr A] goes on to state: *I have been to several Educational Sessions regarding this Zolendronate Infusions. My understanding was that there was a relative precaution regarding Renal Impairment which was accounted for by reducing the rate of the Infusion extending the time of administration. It is my regret that I had not at any stage registered a contra-indication in degrees of severe Renal Impairment. This is also clouded by the Manufacturers Recommendations for Kidney Function are based on 'Creatinine Clearance' but our local Laboratory only reports 'estimated Glomerular Filtration rate' or GFR. These two calculations are not the same thing. [Mrs B's] renal function was very poor with a GFR of 19ml/min. Using an online Cockcroft Gault calculator, this translates through to a Creatinine Clearance of 31 ml/min. The manufacturer of Zolendronate indicates a contra-indication for its use with a creatinine clearance below 30. However, the Aclasta Brand that we use advises not administering with a Creatinine Clearance of below 35.*

(vi) Since the events in question, there has been open disclosure to [Mrs B's] family. The practice has undertaken a retrospective review of all Aclasta infusions over the past five years and [Dr A] states: [We] *identified one other patient whose kidney function was marginal but has several infusions without ill-effect. Three days after [Dr C's] phone call we formalized a process of checking before candidates routinely with Renal Function tests and applying the Cockcroft Gault Formula to ensure the Creatinine Clearance is within guidelines.*

5. Clinical notes review

(i) The response appears largely consistent with the clinical notes. I note [Mrs B's] extensive co-morbidities including her history of chronic renal impairment. In January 2012, she had required ICU admission and haemodialysis for an episode of acute on chronic renal impairment.

(ii) On general review of the notes leading up to the events in question, there was no particular concern raised at the standard of [Mrs B's] care. I note involvement of multiple specialists as her co-morbidities proved increasingly problematic, including

vascular surgeon, endocrinologist, cardiologist, pain specialist, orthopedic surgeon and diabetes clinical nurse specialist. [Mrs B's] renal function was monitored regularly with the previous 12 months' results tabulated in the section below. Most recent height and weight measurements on record were 24 [Month3] with weight 93kg, height 144cm and BMI 44.8 (morbidly obese). This is relevant in that obesity affects calculation of creatinine clearance (see later discussion).

(iii) [Mrs B's] renal function results on file for the 12 months leading up to (and including) her admission are tabulated below:

Date	[Date]	[Date]	[Date]	[Date]	[Date]	[Date]
Na[1] (mmol/L)	142	142	141	142	143	134
K (mmol/L)	5.4	5.1	5.3	5.3	6.1	6.9
Creat (µmol/L)	137	148	159	178	213	536
eGFR (mL/min)	33	30	28	24	19	6

(iv) Consultation notes in [Month10] are:

- 16 [Month10] ([Dr A]) — *pain specialist recommended aclasta but has not organized to see monday to have aclasta here*
- 19 [Month10] ([Dr A]) — *Scanned Aclasta Infusion Consent*
- 19 [Month10] (practice nurse) — *Aclasta infusion cannula inserted and infusion commenced by [Dr A] this is a one off aclasta. pain team had advised she was a good candidate and [Dr A] booked app. no further needed*

(v) The signed Aclasta infusion consent form has been viewed. This includes the standard statements: *I am aware that today I will be receiving a Zolendronic (Aclasta) Infusion. I have had explained to me the purpose, procedure and possible adverse effects. I agree to this procedure taking place.* The form has been signed and dated 19 [Month10]. It is unclear whether [Mrs B] received additional written information regarding the procedure and medication. There is no reference to checking of renal function or calculation of creatinine clearance at this time.

6. The manufacturer information sheet for Aclasta[2] includes the following statements:

(i) *Patients must be appropriately hydrated prior to administration of Aclasta. This is especially important in the elderly and for patients receiving diuretic therapy … The use of Aclasta in patients with creatinine clearance <35 mL/min is contraindicated … No dose adjustment is necessary in patients with creatinine clearance ≥35 mL/min.*

[1] Reference ranges: Na 135–145 mmol/L; K 3.5–5.3 mmol/L; creatinine 45–90 µmol/L; eGFR >60 ml/min
[2] http://www.medsafe.govt.nz/profs/datasheet/a/Aclastainf.pdf Accessed 6 April 2017

(ii) *The use of Aclasta in patients with severe renal impairment (creatinine clearance <35 mL/min) is contraindicated due to an increased risk of renal failure in this population … especially in patients with pre-existing renal impairment or other risk factors including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration occurring after Aclasta administration. Renal impairment has been observed in patients after a single administration. Renal failure requiring dialysis or with a fatal outcome has rarely occurred in patients with underlying renal impairment or with any of the other risk factors described above.*

(iii) *The following precautions should be taken into account to minimise the risk of renal adverse reactions:*

- *Creatinine clearance should be calculated (e.g. Cockroft-Gault formula) before each Aclasta dose. Transient increase in serum creatinine may be greater in patients with underlying impaired renal function; interim monitoring of serum creatinine should be considered in at-risk patients.*
- *Aclasta should be used with caution when concomitantly used with other medicinal products that could impact renal function.*
- *Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of Aclasta.*
- *A single dose of Aclasta should not exceed 5 mg and the duration of infusion should not be less than 15 minutes.*

7. The main clinical indication for Aclasta infusion in primary care is treatment of osteoporosis which is not a listed clinical indication for pamidronate. Completion of a Pharmac Special Authority form is required for funded access to Aclasta. It does not appear a Special Authority Form was completed in [Mrs B's] case, and it is not clear she would have fulfilled the criteria for funded access had a form been completed.

8. Pamidronate was the drug identified to be trialled by the DHB pain service in an attempt to relieve [Mrs B's] bony pain. This has different clinical indications and a different pharmacokinetic profile to Aclasta. The drugs are not interchangeable. In particular, the manufacturers of pamidronate note[3]: *Pharmacokinetic studies indicate that no dose adjustment is necessary in patients with any degree of renal impairment. However, until further experience is gained a maximum infusion rate of 20 mg/h is recommended in renally impaired patients.* It is possible, based on the consultation notes recorded in section 5(iv), that [Dr A] has misinterpreted the pain specialist recommendation for pamidronate (which was clearly named in the specialist letter) as a recommendation for Aclasta.

9. Given the potential for Aclasta to affect renal function, there are clear pre-administration processes outlined in the manufacturer data already discussed. It would be my expectation that a practice regularly undertaking Aclasta infusions has a clear and well documented protocol and check-list for this process. My own practice has separate patient information, consent and pre-procedure check list forms which were

[3] http://www.medsafe.govt.nz/profs/Datasheet/a/aftpamidronateinj.pdf Accessed 6 April 2017

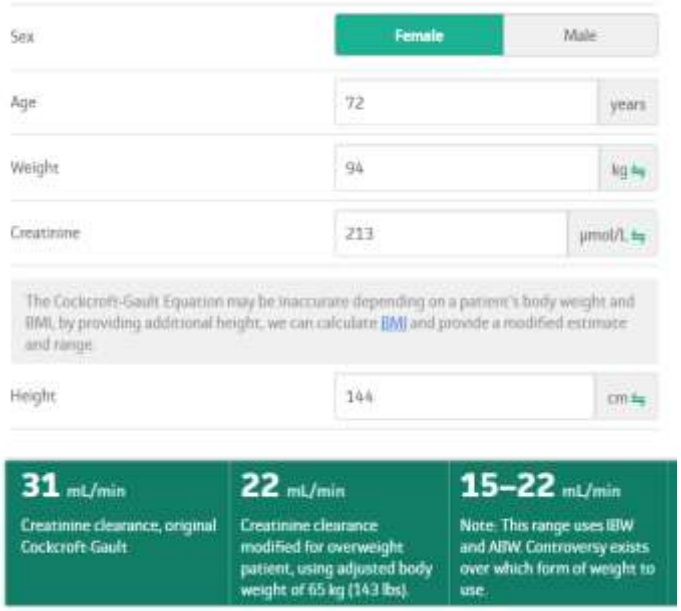
developed with specialist advice and taking into account the drug manufacturer recommendations. These forms are very similar to those used in the Counties Manukau DHB POAC scheme which include recommendations regarding pre-procedure checking of patient's eGFR/creatinine clearance, calcium levels, adequate pre-procedure hydration and stopping diuretics on the morning of the procedure[4]. These recommendations are in line with drug manufacturer information and with additional Medsafe data[5] and BPAC education[6] provided when access to the infusions was granted to primary care in 2010.

10. The Medical Council of New Zealand makes recommendations regarding good prescribing practice[7] including:

- *You should only prescribe medicines or treatment when you have adequately assessed the patient's condition, and/or have adequate knowledge of the patient's condition and are therefore satisfied that the medicines or treatment are in the patient's best interests.*
- *Be familiar with the indications, adverse effects, contraindications, major drug interactions, appropriate dosages, monitoring requirements, effectiveness and cost-effectiveness of the medicines that you prescribe.*
- *Prescribe in accordance with accepted practice and any relevant best practice guidelines.*
- *Keep a clear, accurate and timely patient record containing all relevant clinical findings; decisions made; adverse drug reactions (date, name of medicine and description of reaction); information given to the patient about the medicines and any other treatment prescribed.*

11. [Dr A] refers to [Mrs B's] creatinine clearance which he has calculated using an on-line tool. I have repeated the exercise using a formula which gives a general calculation and then a calculation which adjusts for [Mrs B's] obesity (see below)[8]. Both figures were within the range for which use of Aclasta is contraindicated according to all New Zealand sources consulted (<35 ml/min) and the adjusted result was well below this level. Using a second 'obesity dedicated' calculation tool[9], a result of 24.1 mL/min was obtained.

[4] http://www.primaryoptions.co.nz/page/zoledronate-infusion/ Accessed 6 April 2017
[5] http://www.medsafe.govt.nz/profs/puarticles/zoledronicacidjune2010.htm Accessed 6 April 2017
[6] http://www.bpac.org.nz/BPJ/2010/August/snippets.aspx#zoledronic Accessed 6 April 2017
[7] https://www.mcnz.org.nz/assets/News-and-Publications/Statements/Good-prescribing-practice.pdf Accessed 6 April 2017
[8] https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation Accessed 7 April 2017
[9] http://www.globalrph.com/salazar.cgi Accessed 7 April 2017



12. Based on my review of the documentation on file, and the discussion above, I make the following comments:

(i) I would be moderately critical if [the medical centre] did not have, at the time of [Mrs B's] Aclasta infusion, a robust protocol and checklist which ensured all appropriate pre-infusion testing and patient advice was undertaken, and the patient was provided with sufficient information to make adequately informed consent for treatment. The practice should be asked to provide further detail on the infusion protocol and process in place in [Month10] including any relevant associated practice documentation. The practice should also be asked to provide a copy of the process audit undertaken since the incident in question.

(ii) I am mildly to moderately critical of the standard of clinical documentation noted in section 5(iv) with there being no indication of what advice was provided to the patient, particularly in relation to hydration cautions or other 'safety-netting' advice. If a standard information pamphlet was provided to the patient covering these areas, this comment will be redundant.

(iii) I am severely critical that [Dr A] chose to order the administration of Aclasta infusion to a patient whose renal function was severely impaired either without calculating the patient's creatinine clearance, or if he did make such a calculation, he authorised the infusion when results would have indicated a contraindication to use of the drug. The clinical notes do not suggest there was any calculation of creatinine clearance prior to administration, yet sequential blood results in the previous 12 months had shown progressive deterioration in renal function and the eGFR, at 19 mL/min, was certainly sufficiently concerning to warrant as accurate a determination as possible of creatinine clearance prior to authorizing the infusion. Furthermore, [Mrs B] was taking diuretics which increased her risk of acute renal impairment known to be associated with use of the drug. I do not feel [Dr A] took adequate account of these factors when he authorized the infusion and the absence

of a formal protocol for the infusion process (if this is the case) may have been a contributing factor.

(iv) Measures taken by the practice since this incident (open disclosure, process audit) appear reasonable but I think they should compare their current process documentation with that provided by Counties Manukau DHB (see reference 4) to ensure it is of an adequate standard.

(v) It is not possible for me to determine what role, if any, the Aclasta infusion played in [Mrs B's] rapid deterioration and death in [Month10]. I note she had multiple significant co-morbidities, concurrent urosepsis, and a past history of acute on chronic renal failure requiring ICU admission and haemodialysis without exposure to Aclasta.

13. **Addendum 6 June 2017:** Further information was received from [the medical centre] on 6 June 2017. This comprised the process documentation related to Aclasta infusions prior to the complaint, and the documentation now used. While the current documentation I would regard as meeting expected standards of care, the previous documentation which did not include an infusion protocol or pre-infusion checklist I would regard as being seriously deficient and departing from expected standards of care to at least a moderate degree. I note in the audit result referred to in section 12(i) there were three patients who did not have current renal function results available prior to Aclasta infusion, yet the infusion apparently proceeded and this must be regarded as concerning and I think relates to the absence of a robust pre-infusion protocol or process at the time of those events."