South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Endocrine

MEDICINE REVIEW

1. Executive Summary

Date: 17 September 2017
Medicine (INN): Bisphosphonates
Medicine (ATC): M05BA
Indication (ICD10 code): Hypercalcaemia, including primary hyperparathyroidism (E21.0-4)
Patient population: Adults
Level of Care: Secondary level
Prescriber Level: Medical doctor
NNT: n/a
Current standard of Care: Pamidronic acid
Motivator/reviewer name(s): Dr GA Timothy
PTC affiliation: NA

2. Name of author(s)/motivator(s)

Dr GA Timothy

3. Author affiliation and conflict of interest details

Discovery Health Medical Scheme; Adult Hospital Level Committee (2017-2020); no conflicts declared.

4. Introduction/Background

Effective treatment of hypercalcaemia aims to reduce serum calcium by inhibiting bone resorption, increasing urinary calcium excretion, or decreasing intestinal calcium absorption.

The bisphosphonates are nonhydrolyzable analogues of inorganic pyrophosphate that adsorb to the surface of bone hydroxyapatite and inhibit calcium release by interfering with osteoclast-mediated bone resorption.

Among the currently available agents for the treatment of malignancy-associated, intravenous (IV) zoledronic or pamidronate are the bisphosphonates of choice.

Zoledronic is favoured by some because it is more potent than pamidronate[1] and can be administered over a shorter time period (15 minutes compared with two hours)

To date the choice of drug on the EML has been pamidronic acid, however according to the supplier this is no longer available (since 31 December 2016).

5. Purpose/Objective

- **P:** Adults with moderate to severe hypercalcemia /hyperparathyroidism
- **I**: IV Bisphosphonates- zolidronic and ibandronic
- **C**: Pamidronic
- **O**: Cost effective treatment of moderate to severe hypercalcaemia

6. Methods

Search strategy:

Pubmed, using the following search strategy "Bisphosphonates AND zoledronic and/or Ibandronic and hypercalcaemia" and articles were restricted to systematic reviews and randomised controlled trials.

Evidence synthesis and quality:

The systematic review by Ross et al, 2004[2] used RCTs to review bisphosphonate therapy for hypercalcaemia as well as skeletal morbidity.

For the hypercalcaemia review:

- Mean time to normocalcaemia for all bisphosphonates ranges from 2 to 6 days.
- Pamidronate was found to be more effective than the control, etidronate, mithramycin and low-dose clodronate (600 mg) in achieving normal calcium levels.
- Pamidronate prolongs (doubles) the median time to relapse compared with clodronate and etidronate.
- A dose response is seen with ibandronate (up to 4 mg) and alendronate.
- From a toxicity perspective, bisphosphonates are well tolerated with a low incidence of side effects.
- Drugs with the longest cumulative duration of normocalcaemia were most cost-effective.
- Zoledronate 4 mg was the most costly but most cost-effective treatment (approximately £22,900 per life year gained). The estimates of cost-effectiveness were sensitive to amount of time in hospital.

Bisphosphonate therapy appears cost-effective in the treatment of hypercalcaemia and for the prevention of skeletal morbidity, particularly for patients with breast cancer. The economic evidence reviewed was of limited quality, therefore there is a cautionary note in terms of interpretation of the result.

Looking at a few smaller trials released after the systematic review:

Zoledronic acid — is considered by many to be the agent of choice for malignancy-associated hypercalcaemia because it is more potent and effective than pamidronate. It is available in many countries for treatment of hypercalcaemia of malignancy at a dose of 4 mg IV over at least 15 minutes.

In a pooled analysis of two separate phase III trials involving a total of 275 patients with tumour-induced hypercalcaemia, a single dose of zoledronic (either 4 or 8 mg) normalized the corrected serum calcium concentration in 87 to 88 percent of patients, compared with only 70% of those receiving pamidronate (90 mg)[2]. Additionally, those receiving zoledronic were able to maintain their serum calcium levels for longer (32 to 43 versus 18 days).

Although renal events were reported more frequently with zoledronic than with pamidronate in trials evaluating chronic use of these drugs to treat patients with metastatic bone disease, there was no difference in the frequency of grade 3 or 4 renal toxicity with either drug. The efficacy of the 4 and 8 mg zoledronic doses were similar, but the 4 mg dose was recommended because there was greater renal toxicity with the 8 mg dose (5.2% versus 2.3% with 4 mg) and higher all-cause mortality (33% versus 19%) [3].

Ibandronate — Ibandronate effectively treats hypercalcaemia of malignancy. In combined trials with over 320 patients, ibandronate doses of 2 mg IV administered over two hours normalized serum calcium in up to 67% of patients, and doses up to 6 mg were safe and well tolerated [4,5]. The frequency of response was significantly higher with 4 or 6 mg than with 2 mg (76 to 77% versus 50%), but the duration of response was not dose dependent[5].

Ibandronate appears to be as effective as pamidronate.

Ibandronate (2 or 4 mg IV) was directly compared with pamidronate (15 to 90 mg IV) in a randomized trial involving 72 patients with hypercalcaemia of malignancy[6]. The number of patients responding to both agents was similar (77% and 76% for ibandronate and pamidronate, respectively) but the median time until the serum calcium began to rise again was significantly longer with ibandronate (14 versus 4 days). However, four days is an unusually short duration of effect for pamidronate and may reflect inadequate dosing or the small size of the clinical trial.

7. Alternative agents

- Denosumab is an option for patients with hypercalcaemia that is refractory to zoledronic acid or in whom bisphosphonates are contraindicated due to severe renal impairment.
- Dialysis is generally reserved for those with severe hypercalcaemia.

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [ ] Not confident [ ] Uncertain [X]</td><td></td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?

Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:

Yes [X] No [ ]

List the members of the group.

List specific exclusion from the group:</td><td>Rationale for therapeutic alternatives included:

References:

Rationale for exclusion from the group:

References:</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [x]

Is the option acceptable to key stakeholders?
Yes [ ] No [ ] Uncertain [X]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [X]</td><td>Cost of medicines/ treatment course:
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Zoledronic acid, IV: 4 mg</td><td>R 229.31*</td></tr><tr><td>Ibadronic acid, IV: 4 mg</td><td>R 1041.51**</td></tr></table>*Contract circular HP04-2016ONC
** SEP Database 27 May 2017 - 60% of SEP
- Ibadronic acid, IV, 6 mg: R 1562.26
- Ibadronic acid, IV, 2 mg: R 520.75</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [ ] No [X] Uncertain [ ]</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☒	☐	☐

Recommendation: The Adult Hospital Level Committee recommend that based on the effectiveness of bisphosphonates therapy for hypercalcaemia and the discontinuation of the pamidronic acid in South Africa, alternative bisphosphonate therapy is required. Zoledronic 4mg, IV and ibandronic 2-4 mg, IV are options that may be considered.

Rationale: Evidence of comparable effectiveness of bisphosphonates (pamidronic acid, zoledronic acid and ibandronic acid).

Level of Evidence: II Low quality systematic review, small RCTs

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
☐	☐	☐

VEN status:

Vital	Essential	Necessary
☐	X	☐

NEMLC MEETING OF 1 FEBRUARY 2018:

NEMLC accepted the proposal above and the recommendation to recommend bisphosphonates, IV as a therapeutic class for hypercalcaemia.

Monitoring and evaluation

None

Research priorities

None

References:

1. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001; 19:558.
2. JR Ross,* Y Saunders, PM Edmonds, S Patel,D Wonderling, C Normand and K Broadley . A systematic review of the role of bisphosphonates in metastatic disease. Health Technology Assessment 2004; Vol. 8: No. 4
3. Schwartz LM, Woloshin S. Lost in transmission--FDA drug information that never reaches clinicians. N Engl J Med 2009; 361:1717
4. Ralston SH, Thiébaud D, Herrmann Z, et al. Dose-response study of ibandronate in the treatment of cancer-associated hypercalcaemia. Br J Cancer 1997; 75:295.
5. Pecherstorfer M, Herrmann Z, Body JJ, et al. Randomized phase II trial comparing different doses of the bisphosphonate ibandronate in the treatment of hypercalcemia of malignancy. J Clin Oncol 1996; 14:268.
6. Pecherstorfer M, Steinhauer EU, Rizzoli R, et al. Efficacy and safety of ibandronate in the treatment of hypercalcemia of malignancy: a randomized multicentric comparison to pamidronate. Support Care Cancer 2003; 11:539.