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

MEDICINE REVIEW:

1. Executive Summary

Date:31 October2017
Medicine (INN): Bisphosphonates oral and IV
Medicine (ATC): M05BA
Indication (ICD10 code): Secondary prevention of fragility fractures (M80-; M81-)
Patient population: Reduced bone density is a major risk factor for fragility fractures. Population would be those at risk for fragility fractures. The prevalence of osteoporosis increases markedly with age, from 2% at 50 years to more than 25% at 80 years.
Prevalence of condition:
In South Africa, the incidence of osteoporosis in our white, Asian and mixed-race populations appears to be similar to that of developed countries, although no fracture data exist. As in the USA, hip osteoporosis is less prevalent in our black populations, although vertebral bone mass, and possibly also fracture prevalence, in black and white South Africans appear to be similar.
If extrapolating data from international statistics, it is estimated that around 1.4 million females aged over 50 and 0.6 million males aged over 50 are suffering from osteoporosis. [2]Osteoporosis
affects over 3 million people in the UK.[12] In the UK, 1150 people die every month following a hip fracture.[1]
NNT: n/a
Level of Care: Secondary level
Current standard of Care: Alendronic acid, oral, 10 mg daily for a maximum duration of 5 years.
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

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, with a consequent increase in susceptibility to fragility fracture. Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, where the World Health Organization (WHO) has quantified this as forces equivalent to a fall from a standing height or less.

Primary osteoporosis can occur in both men and women, but is most common in women after menopause, when it is termed postmenopausal osteoporosis. In contrast, secondary osteoporosis may occur in anyone as a

result of medications, specifically glucocorticoids, or in the presence of particular hormonal disorders or other chronic diseases.[1]

There are a number of pharmacological treatments available for the primary or secondary prevention of fragility fractures: oral alendronic acid, oral ibandronic acid, intravenous (i.v.) ibandronic acid, oral risedronic acid and i.v. zoledronic acid. These are all nitrogen containing bisphosphonates.

Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone. Aminobisphosphonate inhibits prenylation of proteins and leads to osteoclast apoptosis, reducing the rate of bone turnover.

Alendronic acid
Alendronic acid is used for treating postmenopausal osteoporosis, orally once daily or weekly. The 10-mg daily dose has also used for treating osteoporosis in men and for preventing and treating glucocorticoid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy (HRT), orally once daily.

Ibandronic acid
Ibandronic acid used for treating postmenopausal osteoporosis, orally once monthly or every 3 months by i.v. injection. Ibandronic acid in the treatment of postmenopausal osteoporosis is administered either by mouth, 150 mg once a month, or by i.v. injection over 15–30 seconds, 3 mg every 3 months.

Risedronic acid
Risedronic acid is used for treating postmenopausal osteoporosis to reduce the risk of vertebral or hip fractures, orally once daily or weekly. It has a marketing authorisation for preventing osteoporosis (including glucocorticoid-induced osteoporosis) in postmenopausal women, orally once daily, and for treating osteoporosis in men at high risk of fractures, orally once weekly. Risedronic acid in the treatment of postmenopausal osteoporosis to reduce the risk of vertebral or hip fractures is administered as 5 mg daily or 35 mg once weekly.

Zoledronic acid
Zoledronic acid is used for treating postmenopausal osteoporosis and osteoporosis in men (including glucocorticoid-induced osteoporosis in postmenopausal women and men) by i.v. infusion once a year. Zoledronic acid in the treatment of postmenopausal osteoporosis and osteoporosis in men (including glucocorticoid-induced osteoporosis in men and postmenopausal women) is administered by i.v. infusion, 5 mg over at least 15 minutes once a year. In patients with a recent low-trauma hip fracture, the dose should be given ≥ 2 weeks following hip fracture repair.30

This review concentrates on the secondary prevention of fragility fractures. The current standard of care according to the EML hospital level guidelines, includes alendronic acid, oral, 10 mg daily for a maximum duration of 5 years. We were asked to review the other bisphosphonate options available in SA to accommodate for supply chain concerns.

Alendronic acid is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis.
Risedronic acid, raloxifene, strontium ranelate and teriparatide are recommended for women at specific risk of

fracture who cannot take alendronic acid.
Ibandronic acid and zoledronic acid do not have recommendations from NICE for the prevention of fragility fractures.

5. Purpose/Objective i.e. PICO

To evaluate the clinical effectiveness of bisphosphonates for the prevention of fragility fractures.

- **-P** Women aged ≤ 64 years and men aged ≤ 74 years in the presence of risk factors, for example previous fragility fracture; current use or frequent recent use of oral or systemic glucocorticoids; history of falls; family history of hip fracture; other causes of secondary osteoporosis
- **-I** Bisphosphonates
- **-C** No treatment (placebo) or alternate bisphosphonate
- **-O** Prevention of fragility fractures

6. Methods:

a. Data sources

Pubmed, Cochrane, Google

b. Search strategy

((((fragility fractures) Osteoporosis)) AND secondary prevention AND bisphosphonates

From this search strategy, a Health Technology assessment was found on a systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. This systematic review looked at a total of 46 randomised controlled trials (RCTs) for the clinical effectiveness.

c. Excluded studies

The identified systematic reviews included all randomised controlled trials (RCTs) relevant to the research question.

d. Evidence synthesis

The systematic review by Davis et al.[1] aimed to summarize and appraise the clinical effectiveness and safety of bisphosphonates for the prevention of fragility fracture and to assess their cost-effectiveness at varying levels of fracture risk.
This systematic review of the literature including network meta-analyses (NMA) was conducted in order to evaluate the clinical effectiveness and safety of oral [alendronic acid, ibandronic acid and risedronic acid and intravenous (i.v.) [ibandronic acid and zoledronic acid} bisphosphonates in the prevention of fragility fractures. For the clinical effectiveness review, six electronic databases and two trial registries were searched: MEDLINE, EMBASE, The Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science and BIOSIS Previews, Clinicaltrials.gov and WHO International Clinical Trials Registry Platform. Searches were limited by date from 2008 until September 2014.

A review of the existing cost-effectiveness literature was undertaken. In the cost-effectiveness review (economic evaluation and quality-of-life studies), seven electronic databases were searched from 2006 until September 2014: MEDLINE, EMBASE, The Cochrane Library, CINAHL, EconLit, Web of Science and BIOSIS Previews. Additional searches were carried out in October 2014–January 2015 in MEDLINE and EMBASE for adverse events, compliance and EuroQol five dimensions questionnaire to inform the model parameters. A de novo health economic model was constructed using discrete event simulation in order to evaluate the cost-effectiveness of the interventions under assessment.

Pooled RCT data for each bisphosphonate indicated no statistically significant differences in the incidence of upper gastrointestinal (GI) events, no evidence of significant differences in mortality and no significant differences in participants withdrawing because of AEs.

Evidence from single RCTs indicated that the risk of upper GI events was significantly higher in men receiving risedronic acid than in those receiving placebo, that men and women receiving placebo were significantly more likely to die following hip fracture than those receiving zoledronic acid, and that the proportion of men withdrawing because of AEs was significantly higher among those receiving alendronic acid than among those receiving placebo.

Pooled RCT data indicated evidence of influenza-like symptoms associated with zoledronic acid. Single RCT evidence indicated no statistically significant difference in the incidence of atrial fibrillation, bone pain or stroke. Single RCT evidence indicated a statistically significant risk of eye inflammation in the first 3 days following administration of zoledronic acid. All RCTs evaluating zoledronic acid reported no cases of spontaneous osteonecrosis of the jaw.
Adverse events of hypocalcaemia and atypical femoral fracture were not reported outcomes in any RCT of any bisphosphonate.

Femoral neck bone mineral density (BMD) was the most widely reported outcome; fracture was the second most widely reported outcome. Assessment of vertebral fractures within the trials was based on both clinical and morphometric fractures.

A total of 46 RCTs were identified that provided data for the clinical effectiveness systematic review. Alendronic acid was evaluated against placebo in 17 RCTs, while 2.5 mg per day of oral ibandronic acid was evaluated against placebo in three RCTs and against 3 mg per 3 months of i.v. ibandronic acid in one RCT. Daily administration of 2.5 mg of oral ibandronic acid was compared with 150 mg per month oral administration in one RCT, risedronic acid was compared with placebo in 12 RCTs and zoledronic acid was compared with placebo in four RCTs. One RCT evaluated alendronic acid compared with 150 mg per month of oral ibandronic acid, five RCTs evaluated alendronic acid compared with risedronic acid, one RCT evaluated zoledronic acid compared with alendronic acid and one RCT evaluated zoledronic acid compared with risedronic acid. The maximum trial duration was 48 months.

The risk of bias associated with the included RCTs was assessed using the Cochrane risk-of-bias instrument. Attrition ≥10% across treatment groups was evident for 29 (63%) of the included
RCTs. Five trials were reported as either open label or single blind, and were considered at high risk of bias of performance bias.

Efficacy:
Femoral neck BMD was the most widely reported outcome and fracture was the second most widely reported outcome. The majority of included trials reported AEs. Across the included trials there was limited reporting on outcomes of compliance (adherence and persistence), hospitalization and service use, and quality of life.

A total of 27 RCTs provided suitable fracture data for inclusion in the fracture NMA: Nine compared alendronic acid with placebo, compared 150 mg per month of oral ibandronic acid with placebo, one compared 2.5 mg per day of oral ibandronic acid with placebo, nine compared risedronic acid with placebo, three compared zoledronic acid with placebo, one compared alendronic acid with risedronic acid; one compared 150 mg per month of oral ibandronic acid with alendronic acid and one compared zoledronic acid with risedronic acid.

Femoral neck BMD may be considered as a surrogate for fracture outcomes. Analysis of the femoral neck BMD data was of interest in order to confirm that the treatment effects were qualitatively the same. The analysis provided no evidence to suggest different treatment effects according to age or sex, with respect to percentage change in femoral neck BMD.
Based on the NMA, all treatments were associated with beneficial effects on each outcome measure relative to placebo.

Non-vertebral fractures are used as a proxy for fractures of the proximal humerus, as fractures of the proximal humerus are not commonly reported. Two studies presented results for proximal humerus fractures, both considering the effects of risedronic acid against placebo. A standard random-effects meta-analysis of these two studies provided a HR of 0.45 (95% CI 0.13 to 1.41), which was greater than that estimated for non-vertebral fractures from the standard random-effects NMA, (HR 0.65, 95% CI 0.47 to 0.88), and from the class-effects NMA (HR 0.71, 95% CI 0.52 to 0.89), but with considerably more uncertainty.

Safety:
There were no statistically significant differences between treatments in the incidence of upper GI events associated with any oral bisphosphonate compared with placebo when data were pooled across RCTs for each bisphosphonate. Adverse events of hypocalcaemia and atypical femoral fracture were not reported as outcomes by any RCT of any bisphosphonate. A summary of evidence from systematic reviews that include observational data indicates that alendronic acid, risedronic acid and oral ibandronic acid have similar rates of GI toxicity when compared with placebo.

Zoledronic acid may be compromised by renal toxicity, and myalgias and arthralgias are evident in the acute phase following i.v. administration. Intravenous bisphosphonates, especially zoledronic acid, are more likely to predispose patients to osteonecrosis of the jaw.

Bisphosphonates are associated with serious atrial fibrillation, but heterogeneity of the existing evidence and a paucity of information on some agents preclude any definitive conclusions with respect to risk.

The review evidence for the use of bisphosphonates and oesophageal cancer is equivocal.

Cost-effectiveness:
Although a number of published studies were identified that assessed the cost-effectiveness of bisphosphonates, and the quality of those studies was generally good, none of the included studies compared all the bisphosphonate treatments appraisal in a fully incremental analysis as required by the NICE reference case.

The de novo economic model estimates that a strategy of no treatment is predicted to have the greatest net benefit for patients, with an absolute risk <1.5% when using Q Fracture® (QFracture-2012 open source revision, Clinrisk Ltd, Leeds, UK) to estimate absolute risk and valuing a quality-adjusted life-year (QALY)at £20,000.

Alendronic acid is predicted to have the maximum incremental net benefit (INB) from 1.5% to 7.2% and risedronic acid is predicted to have the maximum INB from 7.2% upwards. However, the absolute costs and QALY gains are small in patients with low absolute risk and the probabilistic sensitivity analysis (PSA) suggested that there is considerable uncertainty regarding whether or not no treatment is the optimal strategy until the Q Fracture score is around 5.5% (the mean absolute risk for the eighth risk category for Q Fracture).

The mean INBs for oral bisphosphonate treatment (alendronic acid, risedronic acid and ibandronic acid) compared with no treatment were positive across all FRAX® (web version 3.9; University of Sheffield, Sheffield, UK) risk categories. Intravenous bisphosphonates (ibandronic acid and zoledronic acid) were predicted to have lower INBs than oral bisphosphonates across all levels of absolute risk when estimated using either Q Fracture or FRAX.

e. Evidence quality:
The quality of the meta-analysis and systematic review performed to assess bisphosphonates for prevention of fragility fractures was high. Attrition of ≥10% across treatment groups was evident for 63% of the included RCTs.

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 [X] Not confident [ ] Uncertain [ ]</td><td>See evidence synthesis, above.</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: relates to PICO question- see recommendation below.
Yes [X] No [ ]

List the members of the group: relates to PICO question- see recommendation below.</td><td>Rationale for therapeutic alternatives included: see recommendation, below.</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/ month:
<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><tr><td>Alendronic Acid 10mg dly</td><td>R 19.25*** (4 suppliers)</td></tr><tr><td>Alendronic Acid 70mg wkly</td><td>R 127.82** (12 suppliers)</td></tr><tr><td>Risedronic Acid 35mg wkly</td><td>R125.39 **(2 suppliers)</td></tr><tr><td>Risedronic Acid 150 mg monthly</td><td>R 123.12 ** (1 supplier)</td></tr></table>*Contract circular HP04-2016ONC
** SEP Database 27 May 2017 - 60% of SEP (weighted average price)
*** Contract circular HP09-2016SD</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 recommends that based on the review above on the effectiveness of bisphosphonates therapy for preventing fragility fractures, that oral bisphosphonates be considered as a therapeutic class on the secondary level EML (i.e. alendronic acid 70 mg, risedronic acid 35 mg, alendronic acid 10 mg and risedronic acid 5 mg).

Rationale: Clinically all bisphosphonates reduced the risk of vertebral fractures compared with no treatment. No bisphosphonate was found to be superior to any other at preventing fractures. All treatments were associated with beneficial effects relative to placebo.
Pairwise comparisons between treatments indicated that no active treatment was statistically significantly more effective than any other active treatment for fracture outcomes. For vertebral fractures and percentage change in femoral neck BMD, the greatest effect was for zoledronic acid, although in general the ranking of treatments varied for the different outcomes, with the treatments providing broadly similar effects. There was no evidence to suggest different treatment effects according to age or sex. Oral bisphosphonates have similar rates of gastrointestinal toxicity when compared with placebo; whilst Intravenous bisphosphonates, especially zoledronic acid, are more likely to predispose patients to osteonecrosis of the jaw.
The de novo economic model from the systematic review suggests that the cost-effectiveness of i.v. bisphosphonates (ibandronic acid and zoledronic acid) is less favourable than for oral bisphosphonates with a negative incremental net benefit compared to no treatment; estimated for both i.v. bisphosphonates across all 10 risk categories for both FRAX and QFracture.
Level of Evidence: I Health Technology Assessment

NEMLC MEETINGS OF 1 FEBRUARY 2018 AND 11 APRIL 2019:
NEMLC accepted the proposed recommendations above.

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
☐	X	X

VEN status:

Vital	Essential	Necessary
☐	X	☐

Monitoring and evaluation considerations
None

Research priorities
None

References:

1. Davis S, Martyn-St James M, Sanderson J, Stevens J, Goka E, Rawdin A, et al. A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. Health Technol Assess 2016;20(78).
2. Hough S, Amod A, Ascott-Evans B.H et al. Revised South African clinical guideline for the diagnosis and management of osteoporosis:2017. Journal of Endocrinology, Metabolism and Diabetes of South Africa. Available online at: www.jemdsa.co.za and www.osteoporosis.org.za