zoledronic acid 5mg/100ml solution for infusion (Aclasta) No. (317/06)

Novartis

8 September 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

zoledronic acid 5mg (Aclasta®) is accepted for use within NHS Scotland for the treatment of Paget's disease of bone in patients for whom the use of a bisphosphonate is appropriate.

Zoledronic acid infusion resulted in similar levels of pain relief but greater and more sustained reduction of serum alkaline phosphatase (a marker of bone turnover) than one course of an oral bisphosphonate.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

zoledronic acid 5mg/100ml solution for infusion (Aclasta^{Ò})

Indication
Treatment of Paget's disease of the bone

Dosing information
5mg by intravenous infusion over 15 minutes

UK launch date
June 2006

Comparator medications

Four other bisphosphonates, pamidronate, risedronate, etidronate and tiludronate, and the hormone, calcitonin, are licensed for treatment of Paget's disease of bone.

Cost of relevant comparators

Drug	Treatment course	Cost of course (£)
Zoledronic acid	**5mg iv single dose**	**284**
Tiludronate	400mg orally daily for 3 months	594
Risedronate	30mg orally daily for 2 months	306
Pamidronate	30mg iv weekly for 6 weeks; or 30mg iv, then 60mg every 2 weeks for 6 weeks	160-187
Etidronate	5-10mg/kg orally daily for up to 6 months; or 20mg/kg orally daily for up to 3 months	116-232

Costs from eVadis drug dictionary accessed on 16th June 2006; doses do not imply therapeutic equivalence; iv = intravenous infusion; sc = subcutaneous injection

A repeat course of each bisphosphonate can be given if necessary. These should be given at least two and three months after completion of initial courses of risedronate and etidronate, respectively, and at least six months after initial courses of tiludronate or pamidronate. Repeat courses would be associated with corresponding additional costs.

Summary of evidence on comparative efficacy

Zoledronic acid is a bisphosphonate that inhibits osteoclast-mediated bone resorption and reduces increased bone turnover due to osteoclast overactivity in Paget's disease of bone.

Two identical double-blind studies recruited patients older than 30 years with radiologically-confirmed Paget's disease who had serum alkaline phosphatase (SAP) concentrations ≥2 times the upper limit of normal. They were randomised in a 1:1 ratio to a single zoledronic acid 5mg intravenous infusion over 15 minutes or oral risedronate 30mg daily for 60 days. All patients also received 1g of calcium and 400 to 1000 units of calciferol daily. The primary outcome was the proportion of the modified intention-to-treat population, which comprised all

randomised patients with a baseline and at least one post-baseline SAP measurement, achieving normalisation of SAP or a reduction in excess SAP of at least 75% at 6 months. In both trials these were significantly greater with zoledronic acid compared to risedronate: 97% (85/88) vs. 73% (60/82) in one study and 95% (84/88) vs. 75% (67/89) in the other, with differences (95% confidence intervals (CI)) between treatment groups of 23% (12%, 35%) and 20% (9%, 31%), respectively. Proportions of patients achieving normalisation of SAP at 6 months were also significantly greater with zoledronic acid: 89% vs. 60% and 89% vs. 56%, with treatment differences (95% CI) of 29% (15%, 43%) and 32% (19%, 46%), in the respective studies. In both trials, and a pooled analysis of these, time to first therapeutic response was significantly shorter with zoledronic acid compared to risedronate, with median times of 64 vs. 89 days in the pooled analysis. In both trials, and a pooled analysis of these, brief pain inventory short-form (BPI-SF) pain severity and interference scores decreased from baseline during treatment with both drugs, with no significant differences between them or trends for superiority of one over the other. In a pooled analysis of both studies there were significant differences between zoledronic acid and risedronate groups in mean change from baseline to 3 months, but not 6 months, on the 100-point SF-36 physical functioning score (3.2 vs. -1.7) and physical summary score (1.7 vs. -0.35) and change from baseline to 6 months in general health score (2.6 vs. -2.3). The later analyses did not include adjustments for multiple comparisons (SF-36 changes estimated from graphs).

At the end of these studies patients who had achieved a response with zoledronic acid or risedronate could enter a follow-up observation period during which SAP was measured every six months. In an analysis at median follow-up of about 17 months from the end of the 6-month study 98% (149/152) of patients who had achieved a response with zoledronic acid maintained this compared to 50% (58/115) of patients who had achieved a response with risedronate, with the difference between groups significant.

Summary of evidence on comparative safety

In the analysis of pooled data from the studies described previously significantly more patients reported adverse effects in the first three days of treatment with zoledronic acid than with risedronate: 54% (95/177) vs. 25% (43/172). These were mainly influenza-type illnesses, which occur with intravenous administration of bisphosphonate, and most resolved within four days. Subsequently rates of adverse effects, including renal and gastrointestinal effects, were similar in the two groups. More patients developed hypocalcaemia with zoledronic acid compared to risedronate: 8 vs. 1, although this was asymptomatic for 6 of the patients given zoledronic acid. Both patients who developed symptomatic hypocalcaemia with zoledronic acid had been non-compliant with recommended calcium and vitamin D supplementation. Reduction in mean calcium from baseline to day 10 was significantly greater with zoledronic acid compared to risedronate: -0.2 vs. -0.08 mmol/L. This was accompanied by greater increases in parathyroid hormone with zoledronic acid from baseline to 3 months (16 vs. 11 pg/ml) and to 6 months (7 vs. 2 pg/ml), with the difference at 6 months significant. There have been reports of osteonecrosis of the maxillofacial region with zoledronic acid and pamidronate used in oncology indications. Although there were no reports of this in patients with Paget's disease, the European regulatory authority advises that post-marketing surveillance is necessary.

Summary of clinical effectiveness issues

Zoledronic acid has demonstrated benefits in reducing SAP, a biochemical marker of bone turnover. However, there is no radiological evidence that it improves bone structure or long-term evidence that it improves fracture rates. Currently the Health Services Research Unit of the University of Aberdeen is conducting a study in the UK to investigate whether lowering SAP is accompanied by beneficial effects on the problems associated with Paget's disease such as deafness, progression of arthritis, bone fractures and reduced quality of life. The results may indicate whether reductions in SAP with zoledronic acid would be associated with improved outcomes in practice.

Data on the duration of efficacy and incidence of adverse effects with zoledronic acid in the treatment of Paget's disease are limited to median follow-up of less than two years from time of dosing in the trials described previously, with follow-up of these patients ongoing. There is no experience of retreatment with zoledronic acid after the initial single infusion. In practice long-term efficacy and safety of zoledronic acid in Paget's disease are unknown.

In the trials described previously, the primary outcome was normalisation or reduction of SAP excess by at least 75% at 6 months. The dosing schedule of risedronate for Paget's disease is 30mg daily for two months, repeated if necessary at least two months after the initial course. A second course of risedronate was not given to study patients failing to achieve adequate reduction in SAP with the first course. In practice, where risedronate is used in its licensed dosing schedule, it is possible that the response rate at 6 months may be greater than that observed with risedronate in the trials therefore the difference in the treatment effect relative to zoledronic acid may be less.

In analyses of pooled data from the trials described previously the proportion of patients not achieving the primary outcome with risedronate was greater in the subgroup who had received an oral bisphosphonate as their last previous treatment, 45% (27/60), than in the subgroup who had not received previous treatment for Paget's disease, 14% (11/76), with corresponding non-responder rates for zoledronic acid in the respective subgroups of 4% (2/55) and 2% (2/82). The overall study population included 33% and 45% of patients from the respective subgroups. In practice the magnitude of the improved responder rate with zoledronic acid compared to risedronate may be less in treatment-naïve patients than in those previously treated with oral bisphosphonate.

No trials compare zoledronic acid with the other parenterally administered bisphosphonate, pamidronate, or the orally administered bisphosphonates, tiludronate and etidronate, which are licensed for treatment of Paget's disease. Therefore, efficacy and safety relative to these drugs are unknown.

Summary of comparative health economic evidence

The manufacturer presented a cost-effectiveness analysis comparing zoledronic acid with risedronate for patients with Paget's disease. A decision tree was used to estimate the costs and effects of zoledronic acid versus risedronate. The model follows patients over two years and allows for changes in health states every 6 months. The main data sources were two 6-month trials described previously and an open, extended observation period to these studies. The results of the analysis estimate that treatment of Paget's disease with zoledronic acid instead of risedronate is more effective and cost saving, with these savings estimated at £347 per patient.

The appropriate model, time horizon and perspective were used. The 6 month cycle length of the model may however be too long to capture the changes in the health states of this particular patient population.

The clinical evidence used in the economic evaluation is based on two phase III trials comparing zoledronic acid with the comparator, risedronate. However, SF-36 data that were collected in the trials were not used in the economic evaluation. As there was no statistical difference in the pain quality of life scores, it is unclear that a reduction in SAP levels would improve patients' quality of life in the short term; reductions in fracture rates were not modelled. The resource use and costs used seem appropriate.

Zoledronic acid appears to offer cost-effectiveness similar to other bisphosphonates used in this indication.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer estimates cost savings on the medicines budget of £18K in year 1 rising to £38K in year 5. Savings from reduced fractures are not included. These figures are based on 729 patients receiving zoledronic acid in year 1 and 4,012 in year 5.

Guidelines and protocols

The 2002 guidelines on management of Paget's disease of bone developed on behalf of the Bone and Tooth Society of Great Britain and the National Association for the relief of Paget's Disease with an educational grant from the Alliance for Better Bone Health note that the primary treatment for Paget's disease is inhibition of bone turnover using bisphosphonate. Oral tiludronate (400mg/day for 12 weeks), oral risedronate (30mg/day for 2 months), or intravenous pamidronate (three infusions of 60mg fortnightly or six infusions of 30mg weekly) have all been shown to be effective. As other oral bisphosphonates have greater activity and fewer adverse effects, etidronate is not recommended for management of Paget's disease. In view of the weaker activity, shorter duration of action, and adverse side-effect profile compared to bisphosphonates, calcitonin is not recommended for the first-line management of Paget's bone disease. It may have a role in those patients in whom bisphosphonates are not tolerated or have proven to be ineffective.

Additional information

After review of a resubmission, the Scottish Medicines Consortium (SMC) issued advice on 9th May 2003 that zoledronic acid (Zometa®) is recommended for restricted use within NHS Scotland. Use of this product should be restricted to prescribing by oncologists for **patients with breast cancer and multiple myeloma.** It provides an alternative to other bisphosphonates licensed for prevention of skeletal related events. It may offer some minor advantages in terms of administration. At a local level the decision will rest on weighing up the additional cost against other options available for improving delivery of oncology services.

Zoledronic acid has a broader range of indications than other bisphosphonates available and has shown efficacy in some patients with prostate cancer and non-small cell lung cancer and other solid tumours. The quality of the economic evidence provided is insufficient to demonstrate that the use of this product for these indications is cost effective.

After an Independent Review Panel assessment, the SMC issued advice on 12th January 2004 that zoledronic acid (Zometa®) is not recommended for use within NHS Scotland for the prevention of skeletal related events (SREs) in patients with advanced prostate cancer involving bone. Although zoledronic acid demonstrated a reduction in SREs compared with placebo in these patients, the absolute reduction was small and the study requires caution in accepting this as sufficient evidence to introduce zoledronic acid into standard practice for the treatment of patients with metastatic prostate cancer. An economic case was submitted by the manufacturer but its quality was not judged to be sufficient to support a recommendation that the drug is cost-effective relative to standard practice in Scotland for this particular indication.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 11 August 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted reference was supplied with the submission.

Reid IR, Miller P, Lyles K et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med 2005; 353: 898-908