Scottish Medicines Consortium

Re-Submission

paricalcitol, 5 micrograms/ml and 10 micrograms/ml solution for injection (Zemplar®) No. (288/06)

Abbott Laboratories

06 June 2008

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

paricalcitol solution for injection (Zemplar®) is not recommended for use within NHS Scotland for the prevention and treatment of secondary hyperparathyroidism in patients with chronic renal failure undergoing haemodialysis.

The benefits and adverse effects of paricalcitol are similar to another vitamin D analogue with which it has been compared. The manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

The prevention and treatment of secondary hyperparathyroidism in patients with chronic renal failure undergoing haemodialysis.

Dosing information

Initial dose in microgram equivalent to 1/80th of the intact parathyroid hormone level (iPTH) in pg/ml given intravenously during haemodialysis and not more frequently than every other day. Doses subsequently adjusted to achieve iPTH no more than 1.5 to 3 times the non-uraemic upper limit of normal (150-300 pg/ml) while maintaining corrected calcium <11.2 mg/dL, phosphate <6.5 mg/dL and calcium x phosphate product <65. The maximum dose per haemodialysis given in clinical trials was 40mcg.

Product availability date

19 May 2005

Summary of evidence on comparative efficacy

Paricalcitol is a synthetic biologically active vitamin D analogue which selectively upregulates the vitamin D receptor (VDR) in the parathyroid glands, leading to suppression of parathyroid hormone synthesis and secretion without increasing VDR in the intestine, and it is described as having minimal impact on calcium (Ca) and phosphorus (P) levels.

Two double-blind trials recruited 263 and 197 adults with end-stage renal disease on haemodialysis who had serum iPTH ≥300 pg/ml, corrected calcium ≤11.5 mg/dL and calcium phosphate (Ca x P) product ≤75 mg^2/dL^2 after washout of any vitamin D therapy.

They were randomised in a 1:1 ratio to intravenous paricalcitol 0.04mcg/kg or calcitriol 0.01mcg/kg after each dialysis (three per week) for four weeks, with doses then increased every four weeks by 0.04mcg/kg and 0.01mcg/kg in the respective groups for a maximum of five dose escalations, unless iPTH was reduced by ≥ 50% of baseline or hypercalcaemia (corrected calcium >11.5 mg/dL) or two measurements of elevated Ca x P product (>75 mg^2/dL^2) occurred. Patients were maintained on the maximum dose or the dose of study drug that reduced iPTH by ≥50% of baseline for up to 12 weeks in one study and, in the second study for the remainder of the 24-week study period (i.e. 4-24 weeks depending on time to achieve maintenance or maximum dose). The dose of study drug was reduced to the previous dose level if iPTH was <100 pg/ml for two consecutive weeks, if one incidence of hypercalcaemia occurred, or if all four Ca x P product measurements within a two-week period were elevated. The protocol of the first study was modified mid way through the study to discontinue treatment in patients at first episode of hypercalcaemia or four consecutive elevated Ca x P product measurements. Both studies were primarily designed to compare incidences of the adverse effects, hypercalcaemia and/or elevated Ca x P product, and these results are detailed below in the comparative safety section. Reduction of iPTH to ≤50% of baseline was an additional outcome to assess efficacy in treating secondary hyperparathyroidism.

There were no significant differences between paricalcitol and calcitriol in proportions of patients within the populations who achieved an iPTH ≤50% of baseline. These were >80% in both groups in the first study and, in the second study, were 85% v 76% in paricalcitol and calcitriol groups respectively.

An historical cohort study included vitamin D-naïve patients undergoing haemodialysis at one of over 1000 haemodialysis centres in North America who initiated treatment with paricalcitol or calcitriol between January 1999 and December 2001. In the primary analysis of 29,021 and 38,378 patients in the respective treatment groups, data were censored at the end of the study period or when patients underwent a renal transplant, transferred to another treatment facility or switched from their first vitamin D formulation. There were various significant differences between the groups in baseline demographics, including ethnicity, duration of dialysis, comorbidities, and mean values of iPTH, calcium, phosphate, Ca x P product and albumin. The primary outcome was mortality rate. Over the trial period this was significantly lower in the group of patients initially treated with paricalcitol compared to those initially given calcitriol: 18.0 and 22.3 per 100-person-years, respectively. In further analyses to adjust for confounders, albumin, calcium and phosphate were each independent predictors of survival, as was paricalcitol as initial choice of vitamin D. In continued refinements of analyses to address confounders, the benefit of paricalcitol over calcitriol diminished, leaving open the possibility that unmeasured confounders (e.g. a specific “doctor effect”) may account in part for the survival differences.

A retrospective analysis included data from patients treated at haemodialysis centres in North America who were new-to-dialysis and initiated treatment with paricalcitol or calcitriol between January 1999 and November 2001. Analyses were carried out on data from 50% of patients eligible for inclusion in the analyses selected at random, excluding patients with incomplete data: that is 4611 and 6832 patients initially treated with paricalcitol and calcitriol, respectively. Data were censored at the end of the study period or when patients changed dialysis modality, had a renal transplant or died. There were various significant differences between the treatment groups in baseline demographics, including ethnicity, duration of dialysis, comorbidities, and mean values for iPTH, calcium, phosphate and albumin. The time standardised all-cause hospitalisation rate (defined as number of hospital admissions per years of on-treatment observation time) and time-standardised all-cause hospitalisation days (defined as number of days in hospital per years of on-treatment observation time) were significantly lower in the paricalcitol group compared to the calcitriol group, with 0.642 fewer hospital admissions and 6.84 fewer days in hospital per year.

Summary of evidence on comparative safety

In the two double-blind trials described previously, which compared paricalcitol with calcitriol, the primary outcome was incidence of a single episode of hypercalcaemia (corrected calcium >11.5 mg/dL) and/or Ca x P product >75 mg^2/dL^2. In the first study there was no significant difference between paricalcitol and calcitriol: 64% (83/130) and 68% (90/133), respectively. In the second study the incidence of hypercalcaemia and/or Ca x P product >75 mg^2/dL^2 was significantly greater with paricalcitol compared to calcitriol: 79% (77/98) vs. 65% (64/99). After the blinding of these studies had been broken various post-hoc analyses were conducted in which hypercalcaemia and elevated Ca x P product were defined by different criteria. The majority of these found no significant differences between the treatment groups. In both studies mean calcium and Ca x P product increases from baseline to final assessment were not significantly different between the treatments. Mean calcium increased by 0.7 and 0.8mg/dL with paricalcitol and calcitriol respectively, in the American patients (85% of the trial population) within the first study and in the second study, it increased by 1.0 and 0.7 mg/dL in the respective treatment groups.

Corresponding results for mean Ca x P product were 5.5 and 6.7 mg^2/dL^2 in the American patients within the first study and in the latter study were 9.2 and 9.4 mg^2/dL^2 in the respective treatment groups.

Summary of clinical effectiveness issues

There are no robust data to indicate that paricalcitol would be associated with benefits over calcitriol in practice with respect to efficacy in reducing iPTH or incidence of adverse effects such as hypercalcaemia and hyperphosphataemia. In the first double-blind comparison of these drugs, the proportion of patients achieving a ≥50% reduction in iPTH from baseline was similar with both drugs, as was the proportion of patients experiencing hypercalcaemia and/or elevated Ca x P product. In the similar second study, more patients achieved a ≥50% reduction in iPTH from baseline with paricalcitol compared to calcitriol, however, this was associated with a significantly greater incidence of hypercalcaemia and/or elevated Ca x P product.

The initial dose of paricalcitol used in these trials was based on body weight whereas the current dosage recommendation is based on serum iPTH levels at baseline. There is evidence that, if the current method of dosing had been used in those trials, initial and maintenance doses would have been higher than those actually given based on body weight.

There are no robust data to indicate that paricalcitol would be associated with improved survival or reductions in hospitalisation over calcitriol in practice. The historical cohort study indicating a possible survival benefit with paricalcitol has a number of serious limitations. Some result from non-random assignment to treatment, which may have contributed to the between group significant baseline differences and possibly unequal risks of death in the groups. A further limitation of this study was incomplete data on concomitant calcium- and non-calcium-containing phosphate binder use. There are similar serious limitations for the retrospective comparison of paricalcitol and calcitriol on hospital admissions. Prospective randomised trials are required to provide evidence that paricalcitol would improve survival or reduce hospital admissions in practice compared to calcitriol.

The paricalcitol studies were mainly conducted in the USA. Differences between the USA and Scotland in patient demographics and healthcare services may influence the size of the benefits to be expected with paricalcitol in Scottish practice.

Some Scottish physicians advise that alfacalcidol is the main vitamin D formulation used in Scotland for treatment of hyperparathyroidism secondary to renal disease. There are no direct comparisons of paricalcitol with alfacalcidol, therefore, relative efficacy and safety in practice are unknown.

Summary of comparative health economic evidence

The manufacturer presented a Markov model that covered both IV and oral forms of paricalcitol. This produced estimates for a cost-utility analysis comparing paricalcitol with alfacalcidol, although a comparison with calcitriol was also included. The manufacturer asked for both forms of paricalcitol to be considered for use in haemodialysis patients in stage 5 of chronic kidney disease after oral alfacalcidol had been found to give inadequate control.

RCT data were not used in the economic model to estimate long-term effects on patient health. Instead, the manufacturer estimated the number of hospital admissions and deaths over time for a cohort of patients in the UK and then applied effectiveness estimates for paricalcitol based on U.S. database studies of the use of paricalcitol in routine practice compared to calcitriol.

For IV paricalcitol (5mcg/ml), the results were £8,568/QALY compared to alfacalcidol 1mcg/ml and £592/QALY compared to calcitriol 1mcg/ml. The economics case submitted was similar to the one made when the SMC did not recommend the medicine in 2006. None of the issues identified then were resolved in the resubmission. The main weaknesses identified were that the clinical evidence is non-randomised, comes from a U.S. setting that may not be typical of Scotland, and involves assumptions about the equivalence of alfacalcidol and calcitriol. For example, the manufacturer suggests that, in a U.S. non-randomised comparison, patients on IV paricalcitol had a 32% lower rate of hospital admissions than patients on IV calcitriol; the submission assumes this 32% reduction would also apply if Scottish patients switched from IV alfacalcidol to IV paricalcitol. However the baseline admission rate in the U.S. study was 2.6 per patient per year whereas by the manufacturer's own estimate the rate in UK patients is 1.0 per patient per year. This raises concerns about the relevance and applicability of the clinical data used.

Summary of patient and public involvement

A Patient Interest Group submission was not made.

Additional information: guidelines and protocols

The National Kidney Foundation Kidney Disease Outcome Quality Initiative includes clinical practice guidelines dated 2003 which recommend the following target ranges for patients with renal failure (CKD Stage 5):

- IPTH 150 to 300 pg/ml (16.5 to 33.0 pmol/L) [Evidence-based]
- Serum phosphorus 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L) [Evidence-based]
- Serum calcium (corrected) within the normal range for the laboratory used, preferably toward the lower end i.e. 8.4 to 9.5mg/dL (2.10 to 2.37 mmol/L) [Opinion]
- Serum Ca x P product < $55mg^2/dL^2$ [Evidence-based] and this is best achieved by controlling serum levels of phosphorus within the target range [Opinion].

The National Institute for Health and Clinical Excellence (NICE) is developing a guideline on chronic kidney disease that is expected to be published in September 2008.

In January 2007, the National Institute for Health and Clinical Excellence published a technology appraisal on cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy. Cinacalcet is not generally recommended for treating people on dialysis who have hyperparathyroidism because of their kidney disease. However, it is recommended for people on dialysis who (i) have very high levels of parathyroid hormone in their blood that cannot be lowered by other treatments and (ii) cannot have an operation to remove the parathyroid glands (a parathyroidectomy), because of the risks involved. It noted that people who do receive cinacalcet should have regular checks. Treatment should be stopped if the parathyroid hormone levels in their blood do not fall substantially within 4 months.

Additional information: previous SMC advice

After review of a full submission the SMC issued advice in August 2006 that paricalcitol solution for injection (Zemplar®) is not recommended for use within NHS Scotland for the prevention and treatment of secondary hyperparathyroidism in patients with chronic renal failure undergoing haemodialysis. The benefits and adverse effects of paricalcitol are similar to another vitamin D analogue with which it has been compared. The economic case has not been demonstrated.

Additional information: comparators

Two other parenteral preparations of vitamin D can be administered with haemodialysis to treat hyperparathyroidism associated with chronic renal failure, calcitriol and alfacalcidol. Calcitriol is the biologically active form of vitamin D3 and alfacalcidol is converted in the liver to calcitriol.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Paricalcitol	**1.5 to 12 micrograms IV three times a week**	**1934 to 5803**
Calcitriol	0.5 to 3 micrograms IV three times a week	891 to 2672
Alfacalcidol	1 to 4 micrograms IV three times a week	336 to 1283

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 10th April 2008. IV=intravenous

Doses for calcitriol are based on usual dosing range in summary of product characteristics (SPC): the maximum dose of 8mcg per dialysis would cost £7,126 annually
Doses for alfacalcidol are based on the usual maintenance dose range in SPC
Doses for paricalcitol are based on 1:3 to 1:4 dose ratios of calcitriol to paricalcitol used in clinical trials: the maximum dose of 40mcg per dialysis would cost £15,475 annually.

Additional information: budget impact

The manufacturer estimated the net impact on the medicines budget at £380k in year 1 and £512k in year 5, based on estimated patient numbers of 201 - 243 in year 1 and 242 - 314 in year 5. These figures took into account the costs of alternative oral vitamin D preparations displaced by IV paricalcitol. The estimates were based on all eligible patients receiving IV paricalcitol in preference to alternative preparations and this assumption does not seem plausible. The manufacturer did not provide information on the proportion of patients estimated to be treated with the oral and IV formulations.

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 16 May 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Sprague S, Llach F, Amdahl M, Taccetta C, Battle D. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. Kidney International 2003; 63: 1483-1490

National Kidney Foundation Guidelines: Kidney Disease Outcome Quality Initiative (K/DOQI). http://www.kidney.org/professionals/KDOQI/guidelines_bone/index.htm Updated 2003. Last Accessed on the 12th of March 2008