paricalcitol, capsules 1,2 and 4 micrograms (Zemplar®) No. (478/08)

Abbott Laboratories

06 June 2008

The Scottish Medicines Consortium 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 full submission

paricalcitol capsules 1, 2 and 4 micrograms (Zemplar®) are not recommended for use within NHS Scotland for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal insufficiency (chronic kidney disease [CKD] Stages 3 and 4) patients and chronic renal failure (CKD Stage 5) patients on haemodialysis or peritoneal dialysis.

The benefits and adverse effects of paricalcitol capsules compared to other vitamin D analogues have not directly been assessed. The manufacturer did not present a sufficiently robust economic analysis 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 (SHPT) associated with chronic renal insufficiency (chronic kidney disease [CKD] Stages 3 and 4) patients and chronic renal failure (CKD Stage 5) patients on haemodialysis or peritoneal dialysis.

Dosing information

Paricalcitol should be administered once a day, either daily or three times a week taken every other day.

For patients with CKD Stage 3 or 4 disease, the initial dose is 1-2 micrograms daily or 2-4 micrograms three times a week based on intact parathyroid hormone (iPTH) levels. Subsequent dosing is based on monitoring of iPTH, serum calcium and calcium x phosphorus (Ca x P) product.

In patients with Stage 5 disease the initial dose is based on 1/60 iPTH level up to a maximum of 32 micrograms and the target range for iPTH is 150-300 pg/mL. Dose reduction is recommended below this level or if serum calcium > 11.0mg/dL or Ca x P >70 mg^2/dL^2.

Product availability date

March 2008

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.

Although the oral formulation is licensed for both Stage 3 and Stage 4 chronic kidney disease, the manufacturer has requested that the Scottish Medicines Consortium consider it only for patients with Stage 5 CKD.

One pivotal double-blind trial recruited patients with end stage renal disease (CKD Stage 5) on haemodialysis or peritoneal dialysis in a 2:1 ratio to oral paricalcitol (n=61) or placebo (n=27) if they had intact parathyroid hormone (iPTH) levels ≥ 300pg/mL, serum calcium ≥ 8.0mg/dL and ≤ 10.5mg/dL, and a calcium x phosphorus (Ca x P) product ≤ $65mg^2/dL^2$ after adjustment of phosphate binder therapy and washout of any prior vitamin D therapy. The initial dose of paricalcitol was the microgram equivalent of baseline iPTH pg/mL divided by 60 (iPTH/60) and during a 12-week treatment period dosage adjustments were based on weekly iPTH as well as Ca x P product and investigator judgement.

The mean dose over the entire treatment period was 3.9 micrograms three times per week for subjects with baseline iPTH ≤ 500 pg/ml and 7.6 micrograms three times per week for subjects with baseline iPTH > 500 pg/ml.

The primary efficacy outcome was the proportion of patients with ≥ 30% reduction in iPTH on two consecutive occasions, and this was achieved by a significantly greater proportion of patients in the paricalcitol group compared with placebo – 51/58 (88%) versus 3/24 (12%) regardless of dialysis modality. Outcomes relating to serum calcium and Ca x P product are

discussed in the safety section. Changes in biochemical markers of bone turnover were consistent with a decrease in bone activity with paricalcitol and an increase with placebo.

Results were pooled for 225 patients in three supportive studies with a similar design to the above trial but with dosage adjustment in 2 microgram steps. These significantly favoured paricalcitol for the proportion of subjects with two or four consecutive ≥ 30% decreases in iPTH (90% versus 6% and 78% versus 2% respectively).

Summary of evidence on comparative safety

In the main placebo-controlled trial there was no significant difference between groups for the primary safety analysis in which the proportion of patients with ≥ 2 consecutive serum calcium measurements > 11.0 mg/dL was 1/61 (2%) with oral paricalcitol and 0/26 with placebo. Values of serum calcium increased with placebo and decreased with paricalcitol, while serum Ca x P product increased to a greater extent with paricalcitol (17%) than with placebo (4.4%) and the difference was significant for both measures.

The pivotal study does not give details of adverse event (AE) reporting. In the pooled analysis of three studies the incidence of AEs was similar between paricalcitol and placebo, and the most common adverse events were pain, abdominal pain, infection, nausea, hypotension, diarrhoea and vomiting.

Summary of clinical effectiveness issues

No direct comparative data are available between oral paricalcitol and any other vitamin D analogue.

While data are available concerning the effect of paricalcitol on biochemical markers of SHPT there is no information relating to its effects on survival, hospitalisation or quality of life.

The paricalcitol studies were mainly conducted in the U.S. 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.

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 American database studies of the use of paricalcitol in routine practice compared to calcitriol.

For oral paricalcitol (14mcg/week), the results were £10,292 per QALY compared to oral alfacalcidol 3.5mcg/week and £9,593/QALY compared to oral calcitriol 3.5mcg/week.

The main weakness was that none of the clinical data used in the model related to the oral formulation so data on IV paricalcitol and calcitriol were used to make comparisons between oral paricalcitol and alfacalcidol. This introduces very considerable uncertainty into the economic calculations. Additionally, the clinical evidence that was used in the model was from a non-randomised study from the U.S. and may not be typical of Scottish practice. Further, it is not clear if oral alfacalcidiol would be an appropriate comparator given the place in therapy that the manufacturer has proposed.

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 $<55 mg^2/dL^2$ [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 resubmission SMC issued advice in June 2008 that paricalcitol (Zemplar®) [solution for injection] 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.

Additional information: comparators

Two other oral preparations of vitamin D can be administered to treat hyperparathyroidism associated with chronic renal failure, calcitriol and alfacalcidol. Calcitriol (1α,25-$(OH)_2$D3) is the biologically active form of vitamin D3 and alfacalcidol (1α-(OH)D3) is converted in the liver to calcitriol.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Paricalcitol	**4-8 micrograms three times a week (every other day)**	**1548 to 3095**
Calcitriol	0.5 to 1micrograms orally daily	134 to 267
Alfacalcidol (non-proprietary)	0.25 to 1 microgams orally daily	90 to 260
Alfacalcidol (One-Alpha)	0.25 to 1micrograms orally daily	41 to 106

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 9th April 2008

Doses for calcitriol are based on usual dosing range in the summary of product characteristics (SPC), the maximum dose of 12mcg per week in two to three equal doses would cost £458 annually.

Doses for alfacalcidol are based on the usual maintenance dose range in the SPC.

Doses for paricalcitol are based on mean doses in the pivotal trial, rounded to available strengths for administration three times a week. The maximum dose of 32 micrograms per dialysis would cost £12,380 annually.

Additional information: budget impact

The manufacturer estimated the net impact on the medicines budget at £416k in year 1 and £556k 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 paricalcitol. The estimates were based on all eligible patients receiving oral paricalcitol and this assumption does not seem plausible.

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.

Ross E, Tian J, Abboud H, Hippensteel R, Melnick J, Pradhan R, Williams L, Hamm L, Sprague S. Oral paricalcitol for the treatment of secondary hyperparathyroidism in patients on haemodialysis or peritoneal dialysis. *American Journal of Nephrology* 2008;28:97-106.

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