All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Paricalcitol (Zemplar®▼) capsules for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal insufficiency

Abbott Laboratories

Advice No: 1309 – August 2009

Recommendation of AWMSG

Paricalcitol (Zemplar®▼) capsules are not recommended for use within NHS Wales for the 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.

Insufficient evidence of clinical and cost effectiveness was presented for AWMSG to recommend its use within NHS Wales.

This report should be cited as:

ABBREVIATIONS

AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
Ca x P	Calcium-phosphorus
CIC	Commercial in confidence
CKD	Chronic kidney disease
ERA	European Renal Association
ESRD	End-stage renal disease
Euro-DOPPS	European Dialysis Outcomes and Practice Patterns Study
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
iPTH	Intact parathyroid hormone
IV	Intravenous
NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service
NMG	New Medicines Group
PSA	Probabilistic sensitivity analysis
PTH	Parathyroid hormone
QALY	Quality-adjusted life year
SHPT	Secondary hyperparathyroidism
SPC	Summary of Product Characteristics
VDR	Vitamin D receptor
VDRAs	Vitamin D receptor activators
WMP	Welsh Medicines Partnership

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 12th August 2009

The recommendation of AWMSG is:

Paricalcitol (Zemplar®▼) capsules are not recommended for use within NHS Wales for the 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.

Insufficient evidence of clinical and cost effectiveness was presented for AWMSG to recommend its use within NHS Wales.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Paricalcitol (Zemplar ®▼) is indicated for 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[1].

The company have stated that they wish however to focus their submission to the All Wales Medicines Strategy Group (AWMSG) on the use of paricalcitol capsules in CKD Stage 5 haemodialysis patients with SHPT who have failed treatment with alfacalcidol (One-Alpha®) therapy.

Patients 'failing' alfacalcidol are defined as patients with poorly controlled SHPT despite alfacalcidol treatment, patients who cannot tolerate alfacalcidol, or those patients in whom the dose of alfacalcidol is not sufficient to control SHPT but higher doses are limited by hypercalcaemia[2].

2.2 Dosing

Paricalcitol is a soft capsule, which should be administered orally once a day, either daily or three times a week (taken every other day). In patients with CKD Stage 5, paricalcitol should be administered three times a week every other day[1].

In patients with CKD Stage 5, the initial dose (in micrograms) is based on baseline intact parathyroid hormone (iPTH) level (picograms per millilitre)/60, up to an initial maximum dose of 32 micrograms and the target range for iPTH is 150-300 picograms per millilitre. Subsequent dosing should be individualised and based on iPTH, serum calcium and phosphorus levels. Serum calcium and phosphorus levels should be closely monitored after initiation, during dose titration periods and with co-administration of strong P450 3A inhibitors[1].

Further information on dose titration can be found in the Summary of Product Characteristics (SPC)[1].

2.3 Market authorisation date

6th December 2007[2].

2.4 UK Launch date

March 2008[2].

3.0 DECISION CONTEXT

CKD is associated with alterations in serum phosphorus, calcium, and vitamin D levels leading to elevated parathyroid hormone (PTH) levels and the development and progression of SHPT. SHPT is therefore an adaptive response to CKD and most patients with CKD Stage 5, or end-stage renal disease (ESRD), who are undergoing dialysis, will have elevated PTH levels and SHPT of variable severity[3]. Sustained exposure of bone to elevated PTH levels results in osteitis fibrosa, a disease of high bone turnover and accelerated bone resorption[4]. Disorders of mineral metabolism are independently associated with an increased risk of bone disease, vascular and soft-tissue calcification[3,5,6], as well as cardiovascular mortality[7,8,9]. Moderate-to-severe hyperparathyroidism is independently associated with an increased relative risk of death, as well as cardiovascular hospitalisation[4,10].

Treatment of SHPT, in patients with impaired kidney function, aims to manage the levels of phosphate, PTH and calcium. Conventional therapy for SHPT includes dietary modification to reduce phosphate intake, the use of phosphate binders, modification of the dialysis regimen and the use of currently available nonselective vitamin D receptor activators (VDRAs) such as calcitriol (Rocaltrol®) or alfacalcidol (One-Alpha®)[11,12]. Replacement therapy with VDRAs may, however, be limited by the potentially serious adverse effects of hypercalcaemia, hyperphosphataemia and elevated calcium-phosphorus (Ca x P) product[13,14]; the metabolic disturbances implicated in the development and progression of vascular calcification and eventual coronary artery disease[15,16]. Cinacalcet (Mimpara®), an orally administered calcimimetic, has been shown to reduce PTH levels[17]. It is recommended by the National Institute for Health and Clinical Excellence (NICE) but only for the treatment of severe refractory SHPT in patients with ESRD (including those with calciphylaxis), and is often given in conjunction with a non-selective VDRA therapy[18]. In severe hyperparathyroidism, total or partial surgical removal of the parathyroid glands may be needed[3].

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 PTH synthesis and secretion without increasing VDR activity in the intestine. Paricalcitol also upregulates the calcium sensing receptor in the parathyroid glands and therefore reduces PTH levels by inhibiting parathyroid proliferation and decreasing PTH synthesis and secretion, with minimal impact on calcium and phosphorus levels[1]. It has been suggested that the ability to successfully target the parathyroid gland with a selective VDRA that has minimal undesirable effects on calcium absorption in the intestine and metabolism in bone may ultimately help to prevent vascular calcification and cardiovascular disease in people with CKD[4,19]. The intravenous (IV) formulation of paricalcitol has been available for use in dialysis patients over the last decade[4,20], although WMP-sought clinical expert opinion suggests that there is very little used in clinical practice in Wales.

The company suggest that the place in therapy in Wales for paricalcitol capsules is as a second line therapy in CKD Stage 5 haemodialysis patients with SHPT who have failed treatment with alfacalcidol[19]; i.e. patients whose PTH levels are above the recommended UK Renal Association target level of 300 picograms per millilitre despite alfacalcidol therapy, and below 800 picograms per millilitre (a PTH level which qualifies a patient to use cinacalcet in Wales in accordance with NICE guidance)[18,21.].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The evidence relevant to the use of paricalcitol capsules in haemodialysis patients with CKD Stage 5, includes a pivotal phase III randomised controlled trial of 88 patients (of whom 62 were receiving haemodialysis) and data pooled from three phase III supporting trials (which included 150 patients on haemodialysis and 75 patients on peritoneal dialysis). A significantly greater proportion of both haemodialysis and peritoneal dialysis paricalcitol-treated patients compared to those receiving placebo achieved the primary efficacy endpoint of two consecutive decreases (≥30%) in iPTH. A statistically significant decrease in iPTH was seen after one week, with a mean 30% reduction occurring by week three. Primary safety analysis from the pivotal trial found no statistically significant differences between the treatment groups in the proportion of patients who developed clinically meaningful hypercalcaemia (≥2 consecutive serum calcium measurements). The pivotal study does not provide details of adverse events.

In the pooled analysis of the three supporting studies paricalcitol capsules appeared to be well tolerated.

In their submission, the company have presented paricalcitol capsules as a second line therapy (after alfacalcidol 'failure' or intolerance). It is not clear however from the trials available whether the patients were failing/intolerant of a VDRA. In addition the studies compared paricalcitol to placebo when a more appropriate treatment might have been salvage with a VDRA in those who could tolerate vitamin D therapy.

4.2 Review of the evidence on cost-effectiveness

The company submission describes a cost utility analysis of paricalcitol compared against alfacalcidol in haemodialysis patients with CKD Stage 5 who have failed on or are intolerant of alfacalcidol treatment.

The model assumes that paricalcitol treatment improves survival and reduces hospitalisation rates compared with alfacalcidol treatment. The incremental cost per quality adjusted life year (QALY) gained is estimated to be £10,344 over a 10-year time horizon. However, there are several limitations to the model, which warrant cautious interpretation of this estimate. Plausible alternative inputs result in more than doubling of the incremental cost-effectiveness ratio (ICER).

There is a lack of direct comparative data for the oral formulations of paricalcitol and the comparators. Therefore, efficacy data in the model, relating to survival and hospitalisation rates, have been modelled from non-randomised, observational data relating to the parenteral formulations of paricalcitol and calcitriol. It is assumed that calcitriol data represent alfacalcidol data and that the outcomes observed with the use of the parenteral formulations represents that which would be observed with the oral formulations. In the base case analysis, the relative reduction in hospitalisations with paracalcitol, that is derived from the observational data, appears subject to some uncertainty and may bias the model against the comparators. A range of scenarios and one-way sensitivity analyses have been conducted, which indicate that the model is sensitive to some key parameter assumptions. These analyses do not adequately address the combined impact of the uncertainty that is apparent in several key parameters.

5.0 LIMITATIONS OF DECISION CONTEXT

- The company have limited this submission to CKD Stage 5 haemodialysis patients only.
- In their submission, the company have presented paricalcitol capsules as a second line therapy (after alfacalcidol 'failure' or intolerance). There is however no robust evidence from the relevant trials available regarding previous therapy with alfacalcidol.
- There is no direct comparative data with other oral vitamin D receptor activators (e.g. alfacalcidol or calcitriol), or standard therapy in clinical practice for this sub-group of patients. Although the extent to which alfacalcidol would be an appropriate comparator is unclear (due to the sub-group identified as the target population for this submission), it is unlikely that a strategy of no treatment would be an option for many patients.
- Safety and efficacy of paricalcitol capsules in paediatric patients has not been established.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

The company submission included results from randomised controlled trials in patients with CKD, Stages 3 and 4, and patients receiving paricalcitol IV. This assessment however only critiques those trials which relate to dialysis patients (with CKD Stage 5) receiving paricalcitol capsules. Furthermore, the company have requested that consideration of their submission be limited to CKD Stage 5 haemodialysis patients only, although the evidence submitted includes patients receiving peritoneal dialysis[19]. The evidence outlined below summarises a published pivotal phase III randomised controlled trial[14] and pooled data from three phase III supporting trials (data available as posters)[22-25]. Points to note regarding these studies are discussed collectively under section 6.1.3.

6.1 Clinical efficacy

6.1.1 Pivotal study of paricalcitol versus placebo in patients with CKD Stage 5 on haemodialysis or peritoneal dialysis (Study M03-635)[14].

The objective of this phase III prospective, double-blind, placebo-controlled, multicentre study was to evaluate the safety and efficacy of oral paricalcitol capsules for the treatment of SHPT in patients with CKD Stage 5 on dialysis. A total of 88 patients (62 on haemodialysis and 26 on peritoneal dialysis were randomised to paricalcitol or placebo in a 2:1 ratio (61 paricalcitol and 27 placebo). The study had three phases: screening, pre-treatment and treatment. In order to enter into the 12-week treatment phase, patients were required to have iPTH levels ≥300 picograms per millilitre, 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.

No statistically significant differences were detected between treatment groups for any of the baseline demographic characteristics (see Table 1A, Appendix 1). The initial and subsequent doses of paricalcitol were calculated using the baseline and then the previous week's iPTH/60 (up to a maximum of 32 micrograms), as well as Ca x P product and the investigator's judgement. The mean dose (three times a week) over the entire treatment period for patients with baseline iPTH ≤500 picograms per millilitre and baseline iPTH >500 picograms per millilitre were 3.9 and 7.6 micrograms, respectively.

The primary efficacy end point was the achievement of two consecutive ≥30% decreases in iPTH from baseline. The secondary efficacy analyses were the absolute and percentage changes from baseline in iPTH and markers of bone turnover. Safety analyses included exploring the development of clinically meaningful hypercalcaemia and this is discussed in section 6.2.

The primary efficacy endpoint was assessed in only those who had a baseline iPTH and at least two iPTH measurements on treatment. A statistically significant decrease in iPTH was seen after one week, with a mean 30% reduction occurring by week three. A significantly greater proportion of both haemodialysis and peritoneal dialysis paricalcitol-treated patients (83% [33/40] and 100% [18/18], respectively) compared to those receiving placebo (16% [3/19] and 0% [0/5], respectively) achieved the primary efficacy endpoint of two consecutive decreases (≥30%) in iPTH.

Phosphate binder use and mean serum phosphorus levels were not different between the treatment groups. The markers of bone activity improved in the paricalcitol-treated patients and worsened in those receiving placebo. See Table 1A, Appendix 1 for further details of this trial.

6.1.2 Supporting studies of paricalcitol versus placebo in patients with CKD Stage 5 on haemodialysis or peritoneal dialysis (Studies 2001013, 2001014, and 2001015)[22-25].

These three 12-week, double-blind, placebo-controlled, randomised multicentre studies support the pivotal study, M03-635, presented in section 6.1.1; similarly designed to evaluate the safety and efficacy of paricalcitol capsules in reducing elevated iPTH in patients with CKD Stage 5. Two of the studies (2001013 and 2001014) were conducted in patients on haemodialysis[22]; the other study (2001015) was performed in patients on peritoneal dialysis [23].

Overall, 225 patients (haemodialysis: 150; peritoneal dialysis: 75) were randomised in a 1:1 ratio to receive paricalcitol capsules (n=110) or placebo (n=115)[25]. Initial doses of paricalcitol were determined by baseline iPTH/60 up to a maximum dose of 32 micrograms. Dose adjustments (as per protocol) of two micrograms were permitted. Study drug was administered three times per week for 12 weeks[22,23].

Overall, 90% and 78% of paricalcitol patients achieved two or four consecutive ≥30% decreases from baseline in iPTH, respectively, compared to 6% and 2% of placebo patients ($p<0.001$ for both two and four consecutive decreases)[24]. In the paricalcitol group, mean iPTH values started to decrease at week one. A ≥30% mean reduction in iPTH occurred at week three and was observed throughout the remainder of the treatment period. See Table 1A, Appendix 1 for further details of the supporting studies relevant to the patients receiving haemodialysis.

6.1.3 Points to note

- The studies available compare paricalcitol to placebo only. This is however unlikely to reflect true clinical practice as most patients would remain on a VDRA.
- In their submission, the company have presented paricalcitol capsules as a second line therapy (after alfacalcidol 'failure' or intolerance). There is however no information available regarding the patients previous therapy with alfacalcidol.
- In the context of the submission i.e. the treatment of CKD Stage 5 haemodialysis patients; the data was limited to 59 haemodialysis patients in the pivotal trial, and 143 haemodialysis patients in the supporting trials.
- The supporting data has only been published as conference posters.
- Although the company submission included several studies providing data regarding quality of life, including hospitalisation rates and survival, these were in studies solely concerning the IV paricalcitol formulation[19]. Results from the trials relating to patients receiving paricalcitol capsules, were limited to biochemical markers of SHPT only.
- In the pivotal trial Kaplan-Meier analyses were performed to assess time to and duration of iPTH response for paricalcitol-treated patients. The estimated probability of maintaining a 30% or more reduction in iPTH for at least one and two months was found to be 78% and 59%, respectively[14].
- Data from studies are limited to only 12 weeks duration; the authors of the pivotal study12 acknowledge this[14].

- Ad hoc analyses by Gonzalez and colleagues examined the effect of paricalcitol capsules in CKD Stage 5 patients with severe SHPT (a baseline iPTH ≥1000 picograms per millilitre) by analysing pooled data from a subset of participants in the supporting studies (n=26)[23]. The majority (80%, 12/15) of paricalcitol-treated patients achieved the primary efficacy endpoint of at least two consecutive ≥30% decreases in iPTH from baseline compared to none of the 11 placebo patients from the sub-group (p<0.001). Additionally, 73% of the paricalcitol-treated patients achieved four consecutive ≥30% decreases in iPTH from baseline, demonstrating the durability of the response[25].
- Authors of the pivotal study (section 6.1.1) note that as iPTH approaches the target range, individualised dose adjustments may be necessary to achieve a stable iPTH level. Furthermore, in situations in which monitoring of iPTH, calcium or phosphorus occurs less frequently than once per week, a more modest ratio for initial and subsequent doses may be warranted[14].

6.2 Safety

The pivotal study does not provide details of adverse events[14]. Primary safety analysis found no statistically significant difference between the treatment groups in the proportion of patients who developed clinically meaningful hypercalcaemia (≥2 consecutive serum calcium measurements >11mg/dL [paricalcitol: 2% versus placebo: 0%]). A significant difference between the groups for mean changes from baseline to the last on-treatment visit for Ca x P product were observed (from 45.38 to 52.94mg^2/dL^2 [14.3%], and from 42.96 to 44.83mg^2/dL^2 [4.2%] for the paricalcitol and placebo groups, respectively; p=0.029). The mean serum calcium levels remained in the normal range throughout the treatment phase for both treatment groups, but increased minimally during treatment in the paricalcitol group, and decreased in the placebo group, reaching statistical significance at various weeks. A statistically significant difference was also observed between the groups for the mean change in serum calcium at the last on-treatment visit. A mean decrease (-0.22mg/dL) was observed in the placebo group, and a mean increase (0.17mg/dL) was observed in the paricalcitol group[14].

Paricalcitol capsules were developed a number of years following the availability of the IV formulation, and the company highlight in their submission that the adverse reactions experienced by patients administered oral paricalcitol are very similar to those known from administration of the IV formulation[19]. A complete representation of the adverse events can be found in the SPC[1].

In the pooled analysis of the three supporting studies paricalcitol capsules were well tolerated with an adverse event profile similar to that observed for patients administered placebo. Adverse events reported by >5% patients in the paricalcitol group; that were similar between the two treatment groups included: pain, abdominal pain, infection, nausea, hypotension, diarrhoea and vomiting[24].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

See section 7.2 for further details.

- alfacalcidiol (One-Alpha®)
- calcitriol (Rocaltrol®)

7.2 Comparative effectiveness

- There is no direct comparative data with other oral vitamin D receptor activators (e.g. alfacalcidol or calcitriol), or standard therapy in clinical practice for this sub-group of patients. Although the extent to which alfacalcidol would be an appropriate comparator is unclear (due to the sub-group identified as the target population for this submission), it is unlikely that a strategy of no treatment would be an option for many patients.
- Paricalcitol capsules may represent a more convenient and less invasive method of drug administration than the IV formulation. The company suggest that this is reflected by the fact that more than 90% of CKD Stage 5 patients with SHPT in Wales are currently using oral alfacalcidol[19].
- Non-selective VDRAs typically used routinely such as calcitriol and alfacalcidol do not have directly comparable indications to paricalcitol. Both calcitriol (Rocaltrol®) and alfacalcidol (One-Alpha®) soft capsules treat hypocalcaemia, due to their ability to raise serum calcium, but they are not specifically indicated for the treatment of SHPT, and their use can be limited by adverse effects (see section 3.0)[11,12]. Cinacalcet (Mimpara®) tablets are indicated for the treatment of SHPT, but as mentioned previously (see section 3.0) its use is restricted by NICE guidance[17,18]; therefore is not considered an appropriate comparator within the context of this assessment.
- The trials available were conducted in the USA, it is unclear if the patient population and treatment practice are representative of those in Wales.

8.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether the additional benefits offered by paricalcitol capsules over the relevant comparator(s) justify the additional costs and if so, whether the total budgetary impact of supporting the use of paricalcitol capsules is acceptable (see section 9.0).

8.2. Description and critique of the company's submission

The company submission[19] describes a cost utility analysis of paricalcitol in patients with CKD Stage 5, who are undergoing haemodialysis and have SHPT that is poorly controlled with alfacalcidol, or in whom alfacalcidol is poorly tolerated or limited by hypercalcaemia. This represents a sub-population of the licensed indication. The company suggests that paricalcitol should be used as a second-line agent, following failed alfacalcidol treatment and before the use of cinacalcet (corresponding to patients with parathyroid levels between 300 and 800 picograms per millilitre), and that currently there are no treatment options available for such patients. However, in the base case analysis, paricalcitol is compared against alfacalcidol (as it is acknowledged that a strategy of no treatment may not be an option for many patients), and in a scenario analysis it is compared against calcitriol[19].

A Markov model has been developed in which a hypothetical cohort of 1000 haemodialysis patients who are alive and not hospitalised may remain in this health state or progress to states of being hospitalised or death. The model does not consider treatment of the underlying renal disorder, or treatment of the SHPT with parathyroidectomy or cinacalcet.

There are several limitations to the model. No direct comparative data for the oral formulations of paricalcitol and the comparators are available, and no comparative data against alfacalcidol are available. Efficacy data in the model relate to survival and

hospitalisation rates, which have been modelled from non-randomised, observational data relating to the parenteral formulations of paricalcitol and calcitriol.

It is assumed that calcitriol data represent alfacalcidol data and that the outcomes observed with the use of the parenteral formulations represents that which would be observed with the oral formulations. In the base case analysis, the relative reduction in hospitalisations with paracalcitol that is derived from the observational data would appear subject to some uncertainty and may bias the model against the comparators. It is assumed there are no differences between treatments in terms of quality of life and any differences in QALYs that are estimated by the model are due only to differences in the modelled survival with paricalcitol and the comparator.

A range of scenario analyses have been conducted to explore the impact of the assumed doses of paricalcitol and the comparators. However, outcomes are modelled and are not dose-related, and the results of these scenario analyses are as would be expected from simply increasing or decreasing the assumed costs of paricalcitol relative to the cost of the comparators. Only one-way sensitivity analyses have been conducted, which do not adequately address the combined impact of the uncertainty that is apparent in several key parameters.

A copy of the model has been provided to WMP, and the reported outputs have been verified.

8.3 Population

The company submission[19] indicates that a hypothetical cohort of 1000 patients with CKD Stage 5, who are undergoing haemodialysis and have SHPT that is poorly controlled with alfacalcidol, or in whom alfacalcidol is poorly tolerated or limited by hypercalcaemia, has been modelled. This represents a sub-population of patients who would potentially meet the licensed indication for paricalcitol[1].

8.4 Perspective and time horizon

The analysis is conducted from the perspective of NHS Wales. A time horizon of 10 years has been used, as this is assumed to be the maximum expected survival of the patient group that is modelled[19]. This is based on extrapolated data from European Renal Agency data (see section 8.6.1.1). A lifetime time horizon is appropriate.

8.5 Comparator

The model compares paricalcitol at a dose of 14 micrograms per week against alfacalcidol at a dose of 3.5 micrograms per week. Although in the wider licensed indication[1] other oral vitamin D receptor activators (e.g. alfacalcidol or calcitriol) would be appropriate comparators for paricalcitol, the company is making a case for, and the model is stated to represent, the use of paricalcitol in patients who have failed on alfacalcidol (i.e. those who are poorly controlled, or do not tolerate, or are unable to receive a sufficient dose of alfacalcidol without the risk of hypercalcaemia). Therefore, the extent to which alfacalcidol would be an appropriate comparator in the modelled patient group is unclear (although it is acknowledged that a strategy of no treatment may not be an option for many patients).

The basis of the modelled paricalcitol dose (14 micrograms per week) is reported to be the dose of paricalcitol used at 12 weeks in a pivotal 12-week, phase III, randomised, placebo controlled trial conducted in 88 patients[14]. The published abstract for this study indicates that, in patients with baseline iPTH $\leq$500 picograms per millilitre, the mean dose of paricalcitol was 3.9 micrograms three times each week (approximately 12 micrograms/week) and in those with baseline iPTH >500 picograms per millilitre, the

mean dose was 7.6 micrograms three times each week (approximately 23 micrograms/week) over the entire duration of the study[14].

The company submission also reports that the dose of paricalcitol at initiation was 33.6 micrograms/week (presumably the mean)[19], which indicates that estimation of the appropriate dose is complicated by the fact that paricalcitol doses are dependent upon iPTH levels[1] and will change over time in line with patient response to treatment.
Sensitivity analysis has been used to consider the impact of the (cost of) different paricalcitol doses (see section 8.9.2).

The basis of the modelled oral alfacalcidol dose (3.5 micrograms/week) is reported to be the consensus of opinion amongst a panel of UK-based renal physicians who attended a company-organised advisory board meeting[19]. However, this is not verifiable from the information provided in the company submission, which relates only to parentally administered alfacalcidol. Parenteral and oral alfacalcidol are assumed to be dosed on a microgram for microgram basis[19]. This panel of experts is also reported to have considered that the outcomes with alfacalcidol treatment would be the same as those with calcitriol. Confidential market research data were highlighted to AWMSG, and on this basis, alfacalcidol is considered by the company to be the most appropriate comparator[19]. A scenario analysis has been conducted in which paricalcitol is compared against calcitriol (however, it should be noted that the efficacy data for alfacalcidol and calcitriol are both based on calcitriol data, and so the scenario analysis really only compares different costs of the comparator – see section 8.6.1).

8.6 Clinical inputs

8.6.1 Efficacy data

There are no direct comparative studies of paricalcitol against alfacalcidol, and the only trials of paricalcitol against calcitriol have compared the parenteral formulations rather than the oral formulations. Therefore, the clinical trial data described in section 6 is not used to provide efficacy data for the model. Instead, the main efficacy data are modelled based on data from a European renal registry[26], a European study of haemodialysis facilities and their patients[27], and US observational studies[28,29] that are used to provide estimates of survival and hospitalisations in relation to IV formulations of paricalcitol and calcitriol. Therefore, a series of assumptions are used to model efficacy:

i. It is assumed that US-based non-randomised, observational data in patients who received parenteral paricalcitol or parenteral calcitriol[28,29], adequately reflects the expected relative risks of outcomes for patients.
ii. Based on the reported consensus opinion of a company-organised panel of UK-based renal specialists, it is assumed that outcomes with alfacalcidol treatment would be the same as those with IV calcitriol when administered three times a week[17].
iii. It is assumed that outcomes in patients who receive the oral formulation of paricalcitol would be the same as in those who receive the parenteral formulation[19].

8.6.1.1 Survival data

On the basis of the above assumptions, the survival of patients has been modelled as follows. It is reported that data from the European Renal Association (ERA) Registry 2003 annual report[26] has been used to predict the maximum life expectancy of patients on haemodialysis (113 months or 10 years), all of whom are assumed to have been treated with alfacalcidol or calcitriol and so are considered to represent the comparator arm in the model[19].

Survival is modelled as a linear function (i.e. the proportion of patients remaining alive is a linear function of time). This is based on a linear regression based on five observation time points over 60 months. This is a highly unusual, which, if it were not for truncation at zero, would result in a negative number of patients surviving. A more appropriate and better fitting exponential function yields very different absolute survival estimates for paricalcitol and alfacalcidol; however, the overall impact on the incremental cost effectiveness ratios between the two survival functions in the base case analysis is small.

A US-based historical cohort study, which compared three-year survival rates of patients who received IV paricalcitol against those who received IV calcitriol, estimated an adjusted hazard ratio for survival with paricalcitol of 0.84 (95% confidence interval 0.79 to 0.90)[28]. This hazard ratio for survival has been applied to the ERA Registry survival data to estimate the mean survival of patients who receive paricalcitol and calcitriol (assumed to represent alfacalcidol). Based on the linear survival function, this is reported to result in a mean estimated survival of 63 months for paricalcitol recipients compared with 56 months for calcitriol (alfacalcidol) recipients[19]. It should be noted that the authors of this historical cohort study, that is used to derive these survival estimates, indicate that their data do not provide definitive results and imply that confirmation would be required from randomised controlled trials[28].

Based on an exponential function, the modelled median survival for ERA Registry patients used to represent the alfacalcidol is 38 months, compared with 45 months for paricalcitol.

8.6.1.2 Hospitalisation data

On the basis of the above assumptions, hospitalisations have been modelled as follows. The baseline probability of a haemodialysis patient being hospitalised was derived from the European Dialysis Outcomes and Practice Patterns Study (Euro-DOPPS), which recorded a wide range of outcomes data for patients attending a large sample of haemodialysis facilities in five European countries[27]. UK data from this study (based on 443 patient years of follow up) indicate a crude hospitalisation rate of 1.0 per year[27]. It is assumed that all patients providing these data would have been receiving alfacalcidol or calcitriol, and so these data are used to provide the hospitalisation rate for the comparator arm of the model[19].

A US-based patient record study, which compared hospitalisations in patients treated with IV paricalcitol and IV calcitriol[29], has been used to adjust the European hospitalisation data to provide estimates for paricalcitol recipients. The company submission reports that patients who received paricalcitol experienced 0.846 fewer hospitalisations per year compared with those who received calcitriol. Patients who received calcitriol experienced a crude mean of 2.61 hospitalisations each year, which is somewhat more than that reported in the Euro-DOPPS data for the UK (crude rate of 1.0 per year)[27].

In the base case model, therefore, the relative reduction in hospitalisations obtained from the US data has been used (calculated as [2.61 – 0.846]/2.61 = approximately 32% relative reduction in hospitalisation). It should be noted that the absolute reduction of 0.846 hospitalisations per year is based on a per protocol analysis of the patient record data (i.e. data only from patients who received paricalcitol or calcitriol for the entire duration of the observation period). The authors of the published data actually present results based on intention to treat analysis (i.e. hospitalisation rates based on the treatment that patients commenced on), which provides a hazard ratio for hospitalisations with paricalcitol of 0.863, representing a relative reduction in hospitalisations of 13.7%[29].

As previously, the authors of this study also indicate that their data do not provide definitive results and imply that confirmation would be required from randomised controlled trials[29].

8.6.2 Adverse events

There appears to be no consideration of adverse events for any individual treatment in the model. The utility weights used for the state of being hospitalised, as used in a sensitivity analysis, incorporate adjustments based on the occurrence of cardiovascular disease and major and minor fractures, which are considered the most likely reasons for hospitalisation in the modelled patient population[19] (see section 8.6.3). However, these are related to the underlying condition of SHPT rather than being specific to treatment adverse effects.

8.6.3 Utility weights

In the base case model, utility weights are incorporated to represent the state of being a haemodialysis patient only. A sensitivity analysis incorporates a utility decrement for the state of being hospitalised[19]. It is assumed that there are no differences in quality of life due to paricalcitol or calcitriol (alfacalcidol) treatment in themselves.

Haemodialysis treatment is reported to be associated with a reduced quality of life for patients compared with population norms. In the model, haemodialysis patients are assumed to have a utility weighting of 0.66, based on that assumed in a Health Technology Assessment (HTA) of hospital and satellite haemodialysis services for patients with ESRD[30].

For the sensitivity analysis in which a utility decrement is incorporated for the state of being hospitalised, utility decrements associated with what the company considers to be the three main reasons for hospitalisation have been estimated and totalled to determine the impact of hospitalisation compared with non-hospitalised haemodialysis patients. For cardiovascular disease, a utility weight of 0.71, which is reported in the company submission to be that associated with congestive heart failure in the Harvard Cost effectiveness Analysis (CEA) registry, 2006[19]. Nevertheless, this has now changed to the Tufts Medical Centre CEA registry and a search for utility weights for congestive heart failure yields values in the range 0.55 to 0.88, depending on the degree of heart failure and the publication[31].

For major fractures and minor fractures, utility weights associated with hip fracture (0.79) and fracture of the humerus (0.98), respectively, have been assumed based on those values presented as reference case values in a systematic review of utility values in osteoporosis conditions[32]. It has then been assumed that hospitalisation rates due to these three conditions would be equal (33%) and these values have been applied to the utility value of 0.66 assumed for non-hospitalised haemodialysis patients to yield estimates of 0.16, 0.17 and 0.21, respectively, for cardiovascular disease, major and minor fractures. The sum of these (0.54) is assumed to reflect the utility of haemodialysis patients who are hospitalised for any reason, i.e. hospitalisation is assumed to be associated with a decrement in utility weight of 0.12. This decrement in utility per hospitalisation is assumed to apply for one month in the absence of data to guide this.

There are, therefore, a range of assumptions employed regarding utility values that are used to weight survival in the model, which are a source of considerable uncertainty in the analyses.

8.7 Healthcare resource utilisation and cost

8.7.1 Drug costs

The doses of paricalcitol and the comparators that are assumed in the base case model are discussed in section 8.5. These doses have been costed using current published list prices. Other dose comparisons have been tested in sensitivity analyses (see section 8.9.2)[19], but as the modelled outcomes are not linked to doses, these sensitivity analyses relate only to assumed costs.

8.7.2 Treatment of adverse effects

Adverse effects are not specifically considered in the model.

8.7.3 Other resource use and costs

Other resource use and costs relate only to hospitalisations and haemodialysis.

The assumed cost of hospitalisations is based on Scottish data. The mean length of stay per hospitalisation is based on average acute nephrology inpatient stays of 8.5 days[19], at an average cost of £4,476. By chance, this is comparable with the 8.7days mean length of hospital stay reported for the UK as part of the Euro-DOPPS. The company submission assumes that hospitalisations in the modelled patient population are likely to be mainly due to cardiovascular disease, or major fracture (e.g. hip fracture) or minor fracture, which are assumed to occur with equal frequency (at least for estimation of associated utility values)[19]. The extent to which this assumed cost of hospitalisation reflects the true costs of hospitalisations, or adequately captures all relevant resource use and costs for this patient population, is unclear.

Haemodialysis costs are not included in the base case model. All patients undergo haemodialysis. However, as the model predicts greater survival for patients who receive paricalcitol treatment compared with calcitriol (alfacalcidol), paricalcitol recipients would expect to undergo more haemodialysis sessions over time than the comparator recipients. A sensitivity analysis has been conducted in which the costs of haemodialysis are included for each arm. The annual costs of haemodialysis are substantial and are estimated to be £23,504 per patient year based on a 2005 HTA of newer immunosuppressants used in renal transplantation[33]. This cost has not been adjusted to current costs.

8.8 Discounting

Costs and outcomes have been discounted at 3.5% per annum[19], which is the preferred discount rate. Rates of 0% and 6% were explored in sensitivity analyses[19].

8.9 Results

8.9.1 Base case analysis

Over the 10-year time horizon of analysis, the incremental cost per QALY gained with paricalcitol treatment compared with alfacalcidol is estimated by the model to be £10,334. This estimate is based on incremental costs of £2,452 (£17,987 versus £15,535) and a gain of 0.237 QALYs (3.06 versus 2.82)[19].

The discounted incremental costs of £2,452 are composed of additional (undiscounted) drug costs of £8,821 and (undiscounted) saving of £5,480 in hospitalisation costs with paricalcitol compared with alfacalcidol. The costs of haemodialysis are not incorporated in the base case analysis. The gain in QALYs is due to the modelled survival being longer with paricalcitol than with alfacalcidol.

8.9.2 Sensitivity and scenario analyses

A range of scenario analyses have been conducted, which are claimed to consider different weekly doses of paricalcitol compared with alfacalcidol (10.5 micrograms versus 3.5 micrograms, and 21 micrograms versus 7 micrograms), and a scenario of paricalcitol 14 micrograms/week compared against calcitriol 3.5 micrograms/week. However, as efficacy is not linked to dose in the model, and the efficacy data for calcitriol has been assumed for alfacalcidol, these scenario analyses simply represent the impact of different assumed costs for paricalcitol and the comparator, and results are as would be expected.

Several one-way sensitivity analyses have also been conducted. The most significant of these appear to be the assumed relative reduction in hospitalisation with paricalcitol treatment and the incorporation of haemodialysis costs into the model. The impact of the assumed cost per hospitalisation is also noteworthy.

In the base case analysis, the relative reduction in hospitalisation is assumed to be around 32% compared with calcitriol (alfacalcidol). However, this was based on per protocol-type analysis of the observational data[19]. When the relative reduction in hospitalisations is reduced to 13.7% (which is the relative reduction in hospitalisation reported from the same data using an intention to treat-type analysis), the ICER more than doubles to £23,465. The unit cost per hospitalisation in the base case analysis is £4,476, and when explored within the range £0 (implausible) to £5,000, the ICER ranged from £27,276 to £8,350. This demonstrates that small changes in the assumed costs of hospitalisation leads to magnified changes in the resulting ICER, which is important given the uncertainty in the hospitalisation costs assumed in the base case analysis and the uncertainty in the modelled relative reduction in hospitalisations with paricalcitol compared with calcitriol (alfacalcidol). The combined impact of the uncertainty in these parameters, as well as others such as the assumed survival improvement with paricalcitol, has not been explored.

Incorporation of the haemodialysis costs into the analysis increases the ICER to £40,908[1]. This is due to the additional haemodialysis costs that are incurred due to longer survival that is modelled for paricalcitol compared with calcitriol (alfacalcidol).

Incorporating the utility decrement associated with hospitalisation had little impact on the model outputs[19]. The model appears relatively stable to the explored variations in other parameters, but only one-way analyses have been conducted.

8.9.2.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis has not been conducted, which is a limitation given the significant uncertainty that is apparent in several key parameters.

8.10 Review of published evidence on cost-effectiveness

Standard literature searches conducted by the Welsh Medicines Partnership (WMP) have not identified any published evidence on the cost-effectiveness of paricalcitol capsules. Two economic evaluations of paricalcitol intravenous injection have been identified[34,35]. One compared this against calcitriol injection in the USA[34], and one compared this against oral calcitriol and oral or IV alfacalcidol in Germany[35]. There are several differences, beyond the formulation of the drug, between the approaches taken in the analyses presented in the company submission to AWMSG[19] and these published analyses. Both published analyses used a one-year time horizon and the assumption of no difference in survival between the drugs that are compared. In addition, the patient population in which treatments are being compared does not appear to be as specific as that considered in the company submission.

Both published analyses concluded that treatment with paricalcitol was more effective and less expensive than with the comparators[34,35]. However, given the range of issues outlined above, these published analyses appear of little value to the current decision problem.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

The budget impact analysis relates only to the sub-population of haemodialysis patients with CKD Stage 5 who are considered to have failed or be intolerant of first-line alfacalcidol. However, as in the economic analysis, the comparator for paricalcitol in the budget impact analysis is alfacalcidol. Renal Registry data are reportedly used to estimate the numbers of patients on dialysis and the proportion with uncontrolled iPTH levels, and expert opinion has been used to estimate the proportion of these who would have failed on first-line treatment and would be eligible for second-line treatment with paricalcitol. The assumptions of improved survival and reduced hospitalisation rates with paricalcitol as used in the economic analysis, are applied in the budget impact analysis and inform the estimates of the number of patients eligible for treatment over time and cost savings associated with reduced hospitalisations. However, there are several uncertainties in the data used to support these assumptions, which may bias the analysis in favour of paricalcitol and collectively render the company estimates of net budget impact of paricalcitol subject to considerable uncertainty.

9.2 Perspective and time horizon

The budget impact analysis is conducted from the perspective of NHS Wales and considers a time horizon of five years[19].

9.3 Data sources

9.3.1 Incident and prevalent cases

The company submission reports that 324.1 people per million population in Wales undergo haemodialysis based on the data contained within the 2003 Annual Report of the ERA[26]. Although this has not been verified in that reference, it is similar to the unadjusted prevalence estimate of 326.4 people per million population in the 2006 Annual Report[35]. Based on population projections, the company estimates that there are 975 patients in Wales currently receiving haemodialysis[19].

It is estimated from UK Renal Registry data[36] that 34% of haemodialysis patients have uncontrolled serum iPTH, although the basis of this is unclear from the reference. This would be equivalent to 331 of the 975 haemodialysis patients in Wales. Of these, the company submission reported a confidential percentage would be inadequately controlled on their first line vitamin D receptor activator, which equates to 83 patients eligible to receive paricalcitol. Further confidential data provided by the company to AWMSG, however suggests there is some uncertainty in this estimate of 83 patients.

The company submission reports that the incidence rate for patients surviving 91 days of haemodialysis treatment is 81.5 people per million, based on the 2003 ERA data[26]. However, this is not verifiable from the cited reference. The 2006 ERA data suggest an unadjusted incidence of 85.3 per million[36]. Based on population projections, and the assumption that 5% of patients die before 90 days, the company estimates that there would be 257 new patients in Wales in 2009. Of these, 22 patients are estimated to be eligible for paricalcitol treatment, based on the assumptions above regarding uncontrolled iPTH levels and a certain percentage (CIC) being considered uncontrolled on their first-line treatment[19].

Based on the annual survival rates for prevalent and incidence haemodialysis patients, reportedly derived from the UK Renal Registry and ERA Registry data, the net number of patients estimated to receive alfacalcidol (or calcitriol) is 131 in 2009, rising to 144 patients in 2013[19]. As in the economic model, paricalcitol is assumed to improve survival compared with alfacalcidol, based on a US historical cohort study that looked at 36-month survival data for patients receiving parenteral formulations of paricalcitol and calcitriol[7] (see section 8.6.1.1). Therefore, the number of patients estimated to receive treatment with paricalcitol is greater than has been estimated for alfacalcidol (or calcitriol); 137 patients in 2009, rising to 153 patients in 2013[19].

9.3.2 Projected rate of adoption and market share

It is assumed that all eligible patients would receive paricalcitol treatment.

9.3.3 Costs and resource use

As in the economic model, the weekly dose of paricalcitol is assumed to be 14 micrograms and of alfacalcidol 3.5 micrograms. These are costed based on current list prices. In the budget impact analysis, non-surviving patients are assumed to accrue 50% of the costs of treatment.

As in the base case economic model, data from a US-based observational study has been used to assume a relative reduction in hospitalisations with paricalcitol treatment of around 32% compared with calcitriol treatment. Therefore, direct savings arising from reduced hospitalisations has been incorporated into the budget impact analysis. There are several sources of uncertainty in the estimate of the reduction in hospitalisations, which may bias the analysis in favour of paricalcitol (see section 8.6.1.2). In addition, the assumed costs of those hospitalisations would appear subject to uncertainty (see section 8.7.3).

The budget impact analysis does not consider the ongoing costs of haemodialysis, which would be greater with the use of paricalcitol due to the assumed increase in survival of recipients compared with alfacalcidol treatment. The costs of haemodialysis are substantial (estimated as being £23,504 per year using 2005 HTA data[33]).

9.4 Results

The drug acquisition costs for treating all eligible patients with paricalcitol are estimated to be £272,621 in 2009, rising to £305,119 in 2013. The corresponding costs for alfacalcidol are estimated to be £10,426 in 2009, rising to £11,486 in 2013. The company estimates cost savings from hospitalisations avoided with the use of paricalcitol compared with alfacalcidol as being £213,274 in 2009, rising to £237,938 in 2013.

The net budget impact of the use of paricalcitol instead of alfacalcidol (additional drug costs plus cost savings from hospitalisations avoided) is estimated to be £59,348 in 2009, rising to £67,181 in 2013[19] (see Table A).

These estimates would appear subject to a significant degree of uncertainty due to the range of issues discussed above.

Table A. Company-estimated cost impact of paricalcitol versus alfacalcidol[19]

	2009	2010	2011	2012	2013
Paricalcitol drug costs (14 micrograms per week)	£272,621	£299,703	£301,508	£301,508	£305,119
Alfacalcidol drug costs (3.5 micrograms per week)	£10,426	£11,340	£11,413	£11,413	£11,486
Cost savings with reduced hospitalisations for paricalcitol	£213,274	£233,585	£235.036	£235,036	£237,938
Net budget impact of paricalcitol	**£59,348**	**£66,118**	**£66,472**	**£66,472**	**£67,181**

9.5 Sensitivity analysis

No sensitivity analyses have been conducted for the budget impact analysis, which is a limitation due to the apparent uncertainty in several key components of the analysis.

9.6 Relevant comparator costs

Although the company submission makes a case only for the use of oral paricalcitol in haemodialysis patients with CKD Stage 5 who have failed on, or are intolerant of, alfacalcidol[19], the licensed indication for paricalcitol is wider than this[1]. Relevant comparators include other vitamin D receptor activators (alfacalcidol, calcitriol). The licensed indications for these comparators differ to that for paricalcitol, and the SPC should be consulted for further details[11,12]. The calcimimetic agent cinacalcet, is recommended for use by NICE only in patients with very uncontrolled iPTH levels (>800 picograms per millilitre) that are refractory to standard therapy and in whom surgical parathyroidectomy is contraindicated[18]. Cinacalcet may, therefore, not be considered an appropriate comparator to oral paricalcitol.

The initial and maintenance doses of paricalcitol and the comparators should be individually tailored to basleine iPTH level and subsequent response, and also taking account of other relevant biochemical parameters. Therefore, example doses and costs of relevant comparators, based on British National Formulary (BNF) list prices[37], are listed in Table B.

Table B. Example doses and costs of relevant comparators for paricalcitol

Drug	Example dose*	Example annual costs[37]
Paricalcitol (Zemplar®)	4 to 8 micrograms three times per week[14,24]	£1547.52 to £3095.04
Alfacalcidol (One-Alpha®)	0.25 to 1 micrograms daily[11]	£40.88 to £106.17
Calcitriol (Rocaltrol®)	0.5 to 1 micrograms daily[12]	£124.67 to £249.34
This table does not imply therapeutic equivalence of drugs or doses * Example dose for paricalcitol based on range of mean doses observed in clinical trials of the oral formulation[14,24];alfacalcidol dose and calcitriol dose based on usual maintenance doses listed in their respective SPC[11,12].		

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- The UK Renal Registry (established by the Renal Association) provides a focus for the collection and analysis of data on the incidence, clinical management and outcome of renal disease. Currently there is a concentration of data concerning renal replacement therapy, including transplantation, but the Registry will extend to other forms of treatment of renal disease in the future. It is considered a source of comparative data, for audit/benchmarking, planning, clinical governance and research; providing data for bodies such as NHS Trusts, and commissioning authorities[38].
- AWMSG are of the opinion that if accepted for use, a specialist should initiate treatment with oral paricalcitol, and that it would not be suitable for shared care.

10.2 Related advice

- In September 2008, NICE published guidelines on the early identification and management of CKD in adults in primary and secondary care[39].
- In January 2007 NICE recommended cinacalcet for those patients with hyperparathyroidisim due to CKD on dialysis, who have high levels of iPTH refractory to other treatments, and where surgical intervention (parthyroidectomy) is contraindicated[18].
- The UK Renal Association current guidelines relating to CKD include specific sections of the National Service Framework for Renal Services and the latest Quality and Outcomes Framework of the General Medical services contract for general practitioners. They are intended to provide clear guidance for the management of patients with CKD and associated audit measures which can be used to assess performance against a nationally agreed set of outcome measures[40].

10.3 Previous AWMSG advice

- On 27 May 2005, the AWMSG issued a statement that it would be unable to support the use of cinacalcet within NHS Wales.[41]. This has subsequently been superseded by the NICE guidance (TA117) published in 2007[18].

10.4 Ongoing studies

The company highlight in their submission that there are several trials of paricalcitol that are currently under way in the UK and Worldwide. However, it is unlikely that results from these studies will be available within the next six to 12 months. Preliminary results from the study below are expected in November 2009[19].

- M05-741 - The VITAL Study - VITamin D (Paricalcitol) for Albuminuria Lowering study: A Phase II, prospective, randomised, double-blind, placebo-controlled, multicentre study evaluating the safety and efficacy of paricalcitol capsules on reducing albuminuria in type 2 diabetic nephropathy subjects who are currently being treated with renin-angiotensin system inhibitors. The objective of the study is to evaluate the safety and efficacy of paricalcitol capsules on albuminuria reduction in CKD subjects with Type 2 diabetic nephropathy receiving optimal angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) therapy.

10.5 Patient organisation information

A patient organisation submission was made by a member of Friends of Renal Care, Glan Clwyd.

10.6 Medical expert / Clinical expert summary

A summary of medical expert opinion was provided to AWMSG members.

REFERENCES

1. Zemplar®▼ Soft capsules. Summary of Product Characteristics. Abbott Laboratories. Mar 2008. Available at: http://www.emc.medicines.org.uk/. Accessed 10 May 2009.
2. Abbott Laboratories. Form A: Initial appraisal information. Zemplar®▼. Jan 2008.
3. De Francisco ALM. Secondary Hyperparathyroidism: review of the disease and its treatment. *Clinical Therapeutics* 2004; 26(12): 1976-93.
4. Cheng S and Coyne D. Paricalcitol capsules for the control of SHPT in CKD. *Expert Opinion Pharmacother* 2006; 7(5): 617-21.
5. Cozzolino M, Brancaccio D, Gallieni M et al. Pathogenesis of vascular calcification in chronic kidney disease. *Kidney Int* 2005. 68: 429-36.
6. Kettler M, Gross M, and Ritz E. Calcification and cardiovascular problems in renal failure. *Kidney Int* 2005; 67 (Suppl.94): S120-27.
7. Ganesh SK, Stack AG, Levin NW et al. Association of elevated serum PO4, Ca x PO4 Product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 2001; 12: 2131-38.
8. Go AS, Chertow GM, Fan D et al. Chronic Kidney Disease and the Risk of Death, Cardiovascular Events, and Hospitalisation. *N Engl J Med* 2004; 351: 1296-305.
9. Wolf M, Shah A, Gutierrez O et al. Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 2007; 72: 1004-13
10. Joy MS, Karagiannis PC, and Peyeri FW. Outcomes of Secondary Hyperparathyroidism in Chronic Kidney Disease and Direct Costs of Treatment. *Journal of Managed Care Pharmacy* 2007; 13(5): 397-407.
11. One-Alpha®. Summary of Product Characteristics. Leo Laboratories Limited. Jun 2007. Available at: http://www.emc.medicines.org.uk/. Accessed 10th May 2009.
12. Rocaltrol®. Summary of Product Characteristics. Roche Products Ltd. Jun 2008. Available at: http://www.emc.medicines.org.uk/. Accessed 10 May 2009.
13. Lindberg J, Martin K, Gonzalez E et al. A long-term, multicentre study of the efficacy and safety of paricalcitol in end-stage renal disease. *Clinical Nephrol* 2001; 56(4): 315-23.
14. Ross EA, Tian J, Abboud H, et al. Oral Paricalcitol for the Treatment of Secondary Hyperparathyroidism in Patients on Hemodialysis or Peritoneal Dialysis. *Am J Nephrol* 2008; 28:97-106.
15. Block GA, Preston SK, Lazarus JM et al. Mineral metabolism, Mortality, and Morbidity in Maintenance Hemodialysis. *J Am Soc Nephrol* 2004; 15:2208-18.
16. Goodman WG, Goldin J, Kuizon BD et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; 342: 1478-83.
17. Mimpara®. Summary of Product Characteristics. Abbott Laboratories. May 2009. Available at: http://www.emc.medicines.org.uk/. Accessed 10 May 2009.
18. National Institute for Health and Clinical Excellence. Health Technology Assessment (TA117). Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy (Quick reference guide). January 2007. Available at: http://nice.org.uk/nicemedia/pdf/TA117quickrefguide.pdf Accessed 13 May 2009.
19. Abbott Laboratories. Form B: Detailed appraisal information. Zemplar®▼. Mar 2009.
20. Zemplar®▼ Solution for Injection. Summary of Product Characteristics. Abbott Laboratories. Oct 2007. Available at: http://www.emc.medicines.org.uk/. Accessed 13 May 2009.

21. UK Renal Registry Guidelines (4th edition). Available at: http://www.renal.org/pages/pages/guidelines.php Accessed 10 May 2009.
22. Llach F, Qui P, Ross E et al. Paricalcitol (Zemplar) capsule controls secondary hyperparathyroidism in chronic haemodialysis patients. American Society Nephrology Renal Week, 12-17 November 2003, San Diego, California, USA.
23. Qui P, Smolenski O, Fadern S et al. Rapid control of secondary hyperparathyroidism with paricalcitol (Zemplar) capsule in patients on peritoneal dialysis. American Society Nephrology Renal Week, 12-17 November 2003, San Diego, California, USA.
24. Qui P, Gonzalez E, Hippensteel R et al. Paricalcitol (Zemplar) capsule controls secondary hyperparathyroidism in chronic haemodialysis patients. National Kidney Foundation Clinical Nephrology Meetings, April 28 - May 2 2004, Chicargo, Illinois, USA.
25. GonzalezE, Qui P, Silberzweig J et al. Paricalcitol (Zemplar) capsule reduces iPTH in CKD Stage 5 patients with severe SHPT (iPTH ≥1000 picograms per millilitre). American Society of Nephrology Renal Week, 12-17 November 2003, San Diego, California, USA.
26. European Renal Association – European Dialysis and Transplantation Association Registry. Annual Report 2003. Available at: http://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2003.pdf Accessed 09 April 2009.
27. Rayner HC, Pisoni RL, Bommer J, et al. Mortality and hospitalisation in haemodialysis patients in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2004; 19: 108-20.
28. Teng M, Wolf M, Lowrie E, et al. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med 2003; 349: 446-99.
29. Dobrez DG, Mathes A, Amdahl M, et al. Paricalcitol-treated patients experience improved hospitalization outcomes compared with calcitriol-treated patients in real-world clinical settings. Nephrol Dial Transplant 2004; 19: 1174-81.
30. Mowatt G, Vale L, Perez J, et al. Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure. Health Technol Assess 2003; Vol 7, No. 2.
31. Tufts Medical Centre CEA registry. Available at: https://research.tufts-nemc.org/cear/search/search.aspx Accessed 08 April 2009.
32. Brazier JE, Green C, Kanis JA. A systematic review of health state utility values for osteoporosis-related conditions. Osteoporosis Intl 2002; 13: 768-76.
33. Woodroffe R, Yao GL, Meads C, et al. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. Health Technol Assess 2005; Vol 9, No. 21.
34. Schumock G T, Arruda J A, Marx S E, et al. Pharmacoeconomic analysis of paricalcitol and calcitriol in the treatment of secondary hyperparathyroidism in haemodialysis: impact of hospitalisations and survival. Journal of Medical Economics 2007; 10: 393-409.
35. Rosery H, Bergemann R, Marx S E, et al. Health-economic comparison of paricalcitol, calcitriol and alfacalcidol for the treatment of secondary hyperparathyroidism during haemodialysis. Clinical Drug Investigation 2006; 26: 629-38.
36. Ansell D, Feehally J, Feest TG, et al. UK Renal Registry Report 2007; UK Renal Registry, Bristol, UK. Available at: http://www.renalreg.com/reports/renal-registry-reports/2007/ Accessed 09 April 2009.
37. British Medical Association/Royal Pharmaceutical Society of Great Britain. British National Formulary No. 56; September 2008.
38. UK Renal Registry. Available at http://www.renalreg.com/ Accessed 13 May 2009

39. National Institute for Health and Clinical Excellence. Health Technology Assessment (CG073). Early identification and management of chronic kidney disease in adults in primary and secondary care. Available at: http://nice.org.uk/nicemedia/pdf/CG073quickrefguide.pdf Accessed 13 May 2009.
40. UK Renal Association guidelines (4th Edition). Available at: http://www.renal.org/pages/pages/guidelines.php Accessed 13 May 2009.
41. All Wales Medicines Strategy Group Statement (Cinacalcet). 31 May 2005. http://www.wales.nhs.uk/sites3/news.cfm?orgid=371&contentid=3517 Accessed 15 May 2009.

Appendix 1. Additional Clinical Information

Table 1A. Prospective studies of Paricalcitol (Zemplar ®▼) capsules in the prevention and treatment of SHPT associated with CKD Stage 5.

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	
Pivotal Trial[14]	Phase III, double-blind, multi-centre, prospective, randomised trial. Treatment phase 12 weeks	88 patients randomised to paricalcitol or placebo in a 2:1 ratio (62 HD patients; 26 PD patients) The primary efficacy endpoint was evaluated in a total of 58 paricalcitol treated patients (40 HD and 18 PD) and 24 placebo treated patients (19 HD and 5 PD).	Age ≥18 years and on HD three times per week or daily PD for at least two months prior to screening. **Exclusion criteria:** Acute renal failure during the 3 months prior to the screening phase, clinically significant chronic gastrointestinal or liver disease, malignancy, HIV infection, active granulomatous disease, a history of hypersensitivity to vitamin D, or a partial parathyroidectomy within one year of the screening phase. Subjects were also excluded, if they received medications that could potentially affect calcium or bone metabolism (e.g., calcitonin, bisphosphonates, cinacalcet, glucocorticoids), or if there was a history of drug or alcohol abuse within six months prior to the screening phase. Subjects who had been taking a phosphate binder had to have been on a stable regimen for four weeks before the screening visit. Aluminium-containing phosphate binders were not allowed to be used for greater than three weeks during the study; subjects on aluminium-containing phosphate binders greater than three weeks within three months of the screening phase also were excluded.	**Paricalcitol group versus placebo:** Median age: 57yrs versus 58 yrs Gender: Female: 39% versus 19% Male: 61% versus 81% Race: Asian- 5% versus 0% Black- 38% versus 63% Other -1% versus 0% White- 56% versus 37% Median time since first HD (years) 2.25 (0.3-13.5) versus 2.7 (0.6-10.5) Baseline iPTH: 721.4 pg/mL versus 626.8 pg/mL	Paricalcitrol versus placebo administered three times per week 74% (530/713) of doses received by paricalcitol patients were based on the protocol formula iPTH/60; 49% (90/143) were lower, and 27% (49/183) were higher than the ratio iPTH/60 24% (44/183) of paricalcitol doses were withheld.	**Paricalcitol capsules versus placebo:Primary endpoint:** Proportion of patients who achieved two consecutive ≥ 30% decreases from baseline in iPTH A greater percentage of paricalcitol-treated patients achieved the primary efficacy endpoint compared to placebo (p <0.001). 83% (33/40) of HD patients and 100% (18/18) of PD patients achieved the primary efficacy endpoint with paricalcitol treatment versus 16% (3/19) of HD and 0% (0/5) of PD patients in placebo group[19]. **Secondary endpoints:** Absolute and percent changes from baseline in iPTH and markers of bone turnover. The differences between the treatment groups in mean change from baseline to the final visit in all of the biochemical bone activity markers (BSAP, osteocalcin, CTx, and TRAP-5b) were statistically significant (p<0.001) for all bone markers except TRAP-5b where p=0.006). The paricalcitol group experienced mean decreases, while the placebo group experienced mean increases in all of the biochemical bone activity markers. Shift analyses revealed that more paricalcitol-treated subjects (45%, 13/29) experienced normalisation of their high baseline BSAP as compared with the placebo subjects (11%, 1/9) and that no subjects in either treatment group experienced low serum BSAP levels.

BSAP= bone-specific alkaline phosphatise; Ca=calcium; CTx= collagen C-telopeptides; HD=haemodialysis; HIV=human immunodeficiency virus; iPTH=intact parathyroid hormone; ; P=phosphorus; PD=Peritoneal dialysis; pg/mL=picograms per milliliter; SE=Standard deviation; Trap-5b= tartrate resistant acid phosphatase isoform 5b.

Table 1A continued.
Supporting studies of Paricalcitol (Zemplar ®▼) capsules in the prevention and treatment of SHPT associated with CKD Stage 5 in patients receiving haemodialysis.

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	
Llach et al[22]	Two double-blind, multi-centre, placebo controlled, randomised studies Treatment phase 12 weeks	150 HD patients randomised 1:1	ESRD patients ≥18 years old undergoing maintenance HD three times per week for at least one month IPTH ≥300pg/mL Calcium 8.0-10.5mg/dL; Ca x P≤65 No maintenance IV glucocorticoids, calcitonin or other drugs that may affect calcium or bone metabolism To remain on stable dose of phospate binders (either calcium, or non-calcium containing; or a combination of the two)	**Paricalcitol group versus placebo:** Mean age (SE): 56.7yrs (1.80) versus 59.5yrs (1.66) Gender: Female: 38% versus 38% Male: 62% versus 62% Race: Asian- 3% versus 3% Black- 45% versus 58% White- 52% versus 39% Mean time since first HD (years): 4.20 (0.2-27.5) versus 4.50 (0.2-24.2)	Paricalcitol versus placebo Mean dose of paricalcitol three times per week: 8.2 micrograms per dose; (range 0-30.0). Mean days on paricalcitol treatment: 73 (range 5-83).	**Paricalcitol capsules versus placebo:** **Primary endpoint:** Proportion of patients who achieved two consecutive ≥30% decreases from baseline in iPTH levels. 90% (63/70) versus 7% (5/73); p<0.001. **Secondary endpoints:** Proportion of patients who achieved four consecutive ≥30% decreases from baseline in iPTH : 79% (55/70) paricalcitol versus 3% (2/73); p<0.001 Mean change in baseline to final evaluation in iPTH; paricalcitol (n=73) versus placebo (n=77): -38.5% (SE:4.64) versus 26.8% (SE:4.52); p<0.001 Mean change in baseline to final evaluation in BSAP; paricalcitol (n=66) versus placebo (n=70): -12.68 (SE:2.001) versus 10.03 (SE:1.943); p<0.001

BSAP= bone-specific alkaline phosphatise; Ca=calcium; CTx= collagen C-telopeptides; ESRD=end-stage renal disease; HD=haemodialysis; iPTH=intact parathyroid hormone; P=phosphorus,; PD=Peritoneal Dialysis; pg/mL=picograms per milliliter; Trap-5b= tartrate resistant acid phosphatase isoform 5b , SE=Standard deviation.