

## **CONFIDENTIAL UNTIL PUBLISHED**

### **Etelcalcetide for treating secondary hyperparathyroidism**

### **Confidential addendum to Evidence Review Group report**

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## 1 Introduction

Amgen submitted a Patient Access Scheme (PAS) to NICE on 25<sup>th</sup> January 2017. This addendum to the ERG report presents the results of the ERG check on the impact of the proposed PAS on the cost-effectiveness of etelcalcetide for the treatment of secondary hyperparathyroidism. We attempted to replicate the company's analyses from their PAS submission, and also repeated the additional ERG analyses presented in our main report.

## 2 Details of the PAS scheme

The proposed PAS is a simple confidential discount on the NHS list price for etelcalcetide of each vial size (see Table 1). We confirm that the reported PAS prices do represent a [REDACTED] reduction on the reported NHS list price.

Table 1. NHS list price and PAS price for etelcalcetide

Dose (mg)		2.5 mg	5 mg	10 mg
Pack size (vials)		6	6	6
<b>NHS list price</b>	per pack	[REDACTED]	[REDACTED]	[REDACTED]
	per vial	[REDACTED]	[REDACTED]	[REDACTED]
	per mg	[REDACTED]	[REDACTED]	[REDACTED]
<b>PAS price</b>	per pack	[REDACTED]	[REDACTED]	[REDACTED]
	per vial	[REDACTED]	[REDACTED]	[REDACTED]
	per mg	[REDACTED]	[REDACTED]	[REDACTED]
	% reduction	[REDACTED]	[REDACTED]	[REDACTED]

The company reported a weighted average cost at list price ([REDACTED] per mg) and at PAS price ([REDACTED] per mg), based on the distribution of vial usage in the three etelcalcetide trials (20120229, 20120230 and 20120360). The estimated cost at the confirmed NHS list price is higher than the anticipated cost in the company submission ([REDACTED] per mg). The PAS submission therefore presented revised cost-effectiveness results for the NHS list price, as well as for the PAS.

The frequency of dose administration was calculated during the efficacy assessment phase (EAP) of the trials, using the pooled, safety analysis set, which includes all patients who received at least one non-missing dose of etelcalcetide and excludes patients who received commercial cinacalcet. The company stated that three doses were recorded incorrectly (two as 9 mg and one as 9.5 mg), but that these cases were excluded from the price calculations. However, we note that the percentage

distribution of vial doses reported in the PAS submission includes these three cases, with the assumption that they received a 10mg dose. This is a reasonable assumption with little impact on the estimated weighted price.

The dose and vial usage reported in the PAS submission are shown in Table 2. In total, 11,743 doses were administered, between a minimum of 2.5 mg and maximum of 15 mg. The company estimated the distribution of vial usage by assuming use of the minimum number of vials, with no sharing of vials. Based on these data and assumptions, we confirm the company’s estimates of the mean cost per mg of etelcalcetide at the NHS list prices and at the PAS prices.

Table 2. Distribution of dose and estimated vial usage

Dose	Frequency	2.5 mg	5 mg	10 mg
2.5 mg	█	█		
5.0 mg	█		█	
7.5 mg	█	█	█	
10.0 mg	█			█
12.5 mg	█	█		█
15.0 mg	█		█	█
Estimated number of vials		█	█	█
Estimated vial distribution		█	█	█

Subjects enrolled in studies 20120229 and 20120230, and 20120360 randomised to receive etelcalcetide.  
 Safety analysis set: all subjects in the pool who received at least one non-missing dose of etelcalcetide and exclude subjects who received commercial use of cinacalcet.  
 Dose assumed to be given using the minimum number of vials.  
 Three doses were recorded erroneously (1 instance of 9 mg and 2 instances of 9.5 mg), assumed to receive 10mg dose

In summary, estimates of the cost per mg for etelcalcetide are shown in Table 3.

Table 3. Estimated cost per mg for etelcalcetide

	Cost per mg
Anticipated list price in Company Submission	█
Confirmed NHS list (PAS Submission)	█
Proposed PAS price (PAS Submission)	█

### 3 Base case analysis

Pairwise cost- effectiveness results for the company’s base case analysis at the confirmed NHS list price and with the PAS are shown in Table 4. For comparison, we also repeat the results for the anticipated list price that was used in the original company submission. The results that we calculated from the model match those reported in the company’s PAS submission.

Table 4 Cost effectiveness results: company base case at different prices

	Incremental Costs	Incremental QALYs	ICER (£/QALY)
<b>Etelcalcetide (with PB/VD) versus PB/VD alone</b>			
Anticipated list price in CS (████ per mg)	████	0.321	████
Confirmed NHS list price (████ per mg)	████	0.321	████
Proposed PAS price (████ per mg)	£8,738	0.321	£27,251
<b>Etelcalcetide (with PB/VD) versus cinacalcet (with PB/VD)</b>			
Anticipated list price in CS (████ per mg)	████	0.069	████
Confirmed NHS list price (████ per mg)	████	0.069	████
Proposed PAS price (████ per mg)	£1,020	0.069	£14,777

### 4 Sensitivity analyses

We re-ran the company’s deterministic sensitivity analyses. At list price, the results were similar to those in the original company submission. The hazard ratio for mortality had the greatest impact on the results, but ICERs remained above £30,000 per QALY for all input values tested, for both comparisons. With the PAS, however, the ICERs remained below £30,000 per QALY for all input values tested, except for the higher range of the mortality HR in the etelcalcetide vs. PB/VD comparison (**Error! Reference source not found.**). We note that the tornado diagram for telcalcetide vs. cinacalcet in the PAS submission (Figure 4, page 22) did not include cinacalcet dose. We have added this in Figure 1.

Probabilistic sensitivity analysis around the company base case with the PAS also showed less uncertainty over the cost-effectiveness of etelcalcetide than with the list price estimates. At list prices, the estimated probability that the ICER is below £30,000 per QALY is very close to zero for both comparisons. However, with the PAS, this probability is about 70% for the comparison with PB/VD alone and over 90% for the comparison with cinacalcet (Figure 2).

Figure 1. Tornado diagrams: company base case with PAS

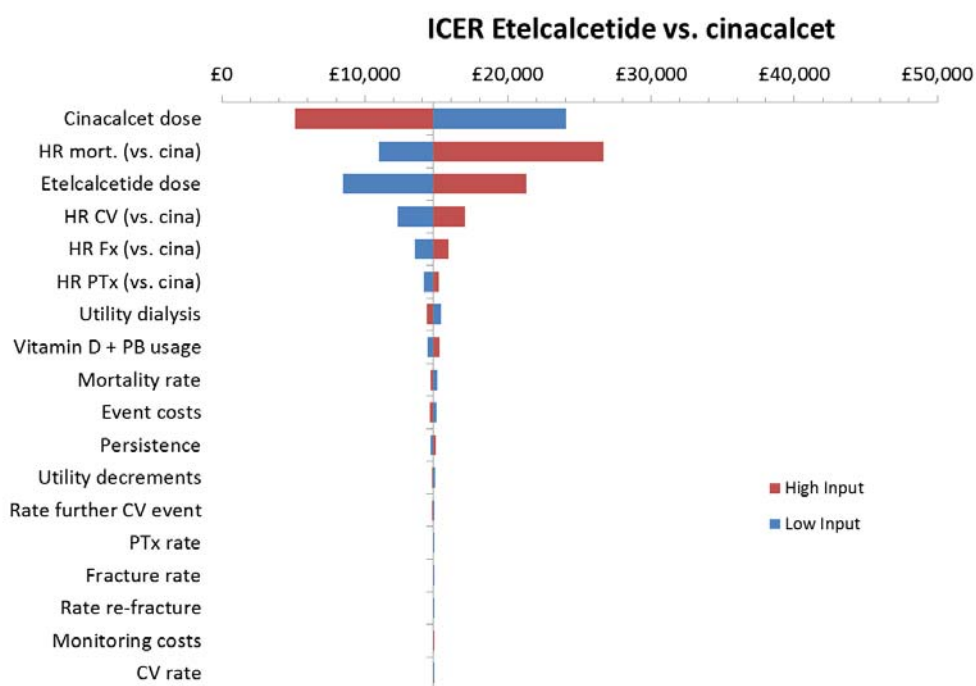
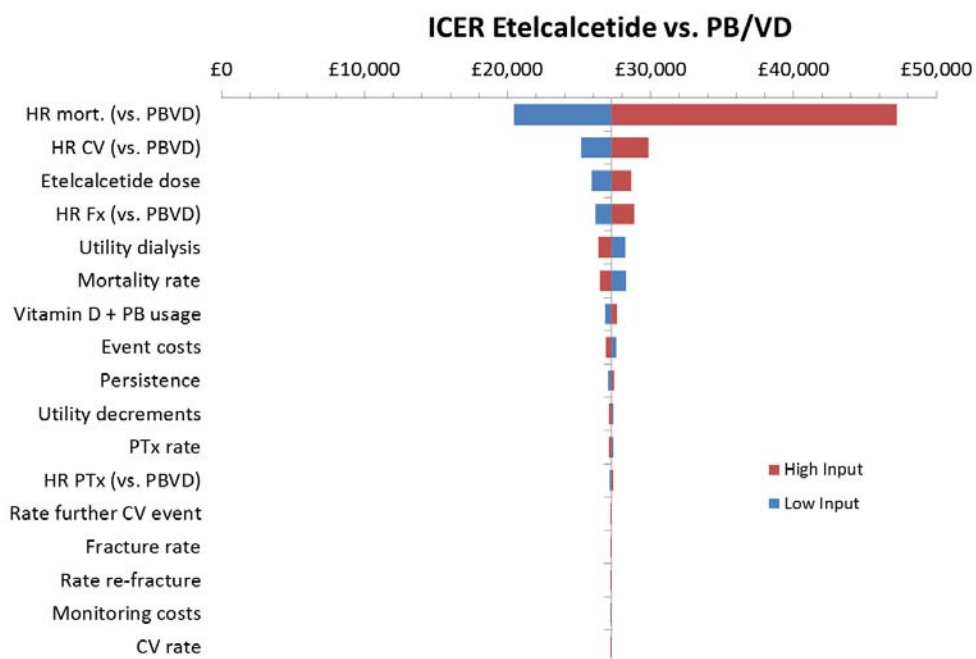
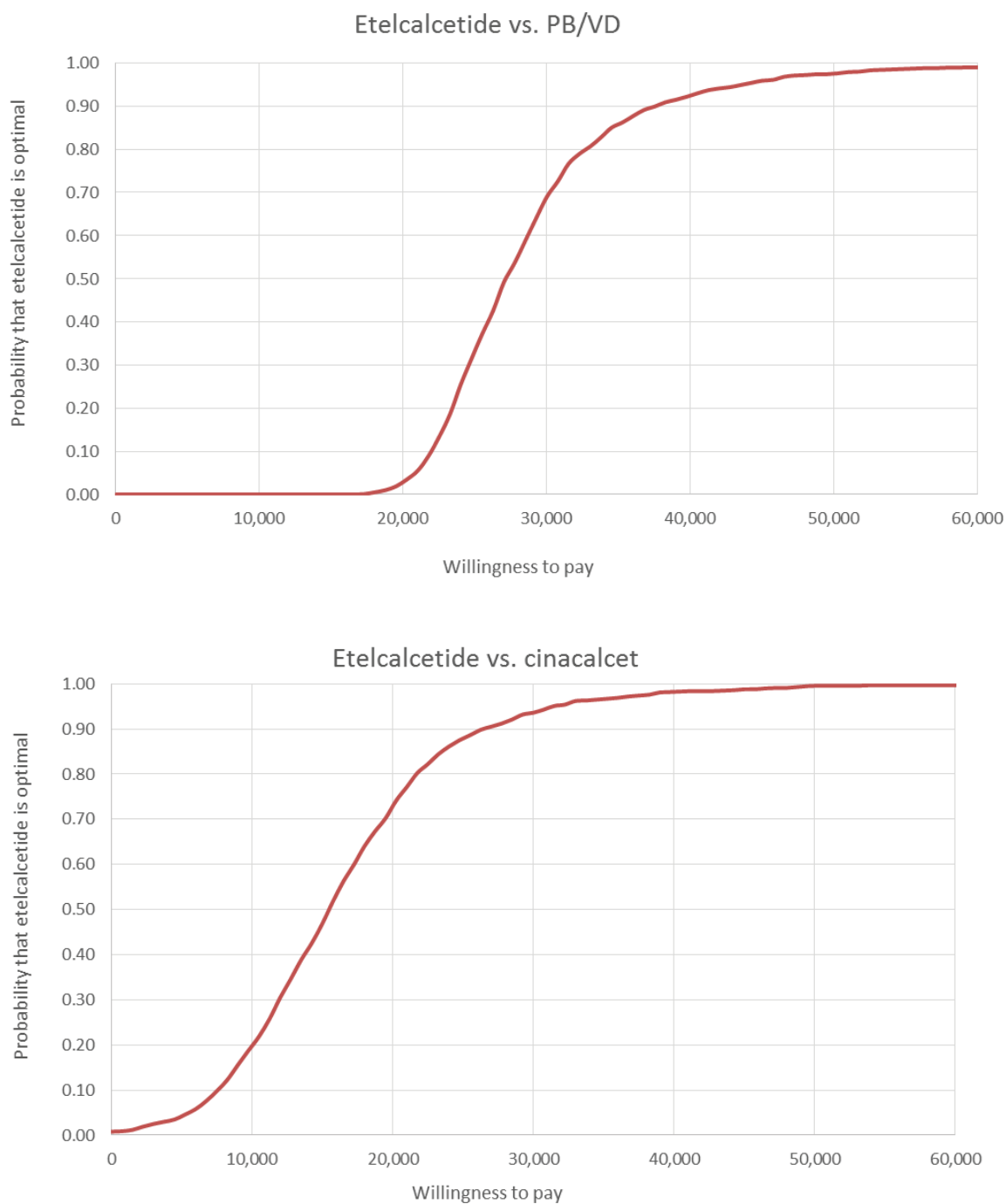


Figure 2. CEACs: company base case with PAS



We also ran the company's scenario analyses with and without the PAS: see Table 5 for the comparison with PB/VD alone and Table 6 for the comparison with cinacalcet. For comparison we

also present the ICERs based on the anticipated list price from the original company submission. At list price, none of the ICERs were below £30,000 per QALY, for either comparison. However, with the PAS the ICERs were less than £30,000 per QALY for almost all of the scenarios tested. The exceptions were:

- the analyses using the Eandi et al risk prediction method to extrapolate trial results in the comparison with PB/VD alone.
- The analyses in which dialysis costs were included, for both comparisons.

Table 5 Company scenario analyses: ICERs for Etelcalcetide vs. PB/VD

Scenario	Anticipated list price (CS)	Confirmed NHS list price	PAS price
<b>Company base case</b>	████████	████████	£27,251
Efficacy: EVOLVE ITT disaggregated	████████	████████	£25,453
Efficacy: Eandi; censored	████████	████████	£36,834
Efficacy: Eandi; ITT disaggregated	████████	████████	£31,857
Age at baseline: 45 years	████████	████████	£28,759
Age at baseline: 65 years	████████	████████	£26,159
PTx: not included (rate=0)	████████	████████	£28,525
Mortality: EVOLVE	████████	████████	£27,490
Discontinuation: Reams et al	████████	████████	£25,144
Discontinuation: Urena et al.	████████	████████	£27,592
Utility: Impact calcimimetic treatment	████████	████████	£23,843
Calcimimetic drug use: EAP; head to head	████████	████████	£28,564
Dialysis costs: included	████████	████████	£61,280
Discount rate: 0%	████████	████████	£23,609
Discount rate: 6%	████████	████████	£29,835

Table 6 Company scenario analyses: ICERs for Etelcalcetide vs. cinacalcet

Scenario	Anticipated list price (CS)	Confirmed NHS list price	PAS price
<b>Company base case</b>			£14,777
Efficacy: EVOLVE ITT disaggregated			£14,622
Efficacy: Eandi; censored			£19,333
Efficacy: Eandi; ITT disaggregated			£15,974
Age at baseline: 45 years			£15,199
Age at baseline: 65 years			£14,504
PTx: not included (rate=0)			£15,271
Mortality: EVOLVE			£14,962
Discontinuation: Reams et al			£13,707
Discontinuation: Urena et al.			£15,053
Utility: Impact calcimimetic treatment			£14,633
Calcimimetic drug use: EAP; head to head			£20,879
Dialysis costs: included			£48,677
Discount rate: 0%			£13,156
Discount rate: 6%			£15,937

## 5 Additional ERG analyses

We repeated the additional ERG analyses presented in Section 4.4.1 of the ERG report, using the updated list price and PAS: see Table 7 and Table 8. In all cases the estimated ICERs remained below £30,000 per QALY with the PAS, except for the analysis in which we applied the direct utility benefit estimated from the analysis of EQ-5D data from the EVOLVE trial only to cinacalcet (assuming no direct benefit with etelcalcetide). In this case, the ICER for etelcalcetide compared with cinacalcet was £42,761 with the PAS.

Table 7 ERG additional analyses: ICERs for Etelcalcetide vs. PB/VD

Scenario	Anticipated list price (CS)	Confirmed NHS list price	PAS price
<b>Company base case</b>			£27,251
Efficacy: simple ITC etelcalcetide trials			£29,730
Efficacy: ≤ 300 pg/mL simple ITC			£25,373
Non-adherence adjustment: IPE method			£25,111



Scenario	Anticipated list price (CS)	Confirmed NHS list price	PAS price
Persistence: 28% at 1 year (Reams et al)	████████	████████	£25,144
Utility gain (0.02) cinacalcet only	████████	████████	£27,251

Table 8 ERG additional analyses: ICERs for Etelcalcetide vs. cinacalcet

Scenario	Anticipated list price (CS)	Confirmed NHS list price	PAS price
<b>Company base case</b>	████████	████████	£14,777
Efficacy: simple ITC etelcalcetide trials	████████	████████	£23,701
Efficacy: ≤ 300 pg/mL simple ITC	████████	████████	£11,490
Non-adherence adjustment: IPE method	████████	████████	£14,292
Persistence: 28% at 1 year (Reams et al)	████████	████████	£13,707
Utility gain (0.02) cinacalcet only	████████	████████	£42,761

The results of the ERG preferred analysis using the updated list price and PAS are summarised in Table 9. The assumptions underlying this analysis are summarised in section 4.4.3.1 of the ERG report (page 136). It combined two main changes to the company base case:

- use of a simple indirect treatment comparison to pool the results of the etelcalcetide trials (rather than the 'naïve' pooling used in the company base case), and
- use of the Iterative Parameter Estimation (IPE) method to adjust EVOLVE data for non-adherence (rather than the lag-censored analysis used in the company base case).

Table 9 ERG preferred analysis

	Incremental Costs	Incremental QALYs	ICER (£/QALY)
<b>Etelcalcetide (with PB/VD) versus PB/VD alone</b>			
Anticipated list price in CS (████████ per mg)	████████	0.325	████████
Confirmed NHS list price (████████ per mg)	████████	0.325	████████
Proposed PAS price (████████ per mg)	£8,879	0.325	£27,290
<b>Etelcalcetide (with PB/VD) versus cinacalcet (with PB/VD)</b>			
Anticipated list price in CS (████████ per mg)	████████	0.044	████████
Confirmed NHS list price (████████ per mg)	████████	0.044	████████

Proposed PAS price (█████ per mg)	£975	0.044	£22,400
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The above analysis assumes that 8.9% of patients would achieve a reduction of >30% in PTH over 6 months without calcimimetic treatment (as in the pooled placebo arms of trials 20120229 and 20120230). However, as argued in section 4.4.3.2 of the ERG report, we consider that it is unlikely that this proportion would be the same for patients who had not responded to PB/VD treatment alone (the ‘refractory’ sub-group for whom cinacalcet is a comparator), as for patients with non-refractory SHPT (for whom PB/VD alone would be appropriate). We therefore repeated our sub-group analysis, assuming that 17.1% and 4.9% of non-refractory and refractory patients, respectively, would achieve >30% PTH reduction without calcimimetic. The results are shown in Table 10, and suggest that the following the ERG preferred analysis, the ICER would be below £30,000 per QALY for both comparisons.

Table 10 ERG preferred analysis with ‘refractory’ and ‘non-refractory’ subgroups

	Incremental Costs	Incremental QALYs	ICER (£/QALY)
<b>Non-refractory to PB/VD alone (17.1% PTH response): Etelcalcetide (with PB/VD) versus PB/VD alone</b>			
Anticipated list price in CS (█████ per mg)	█████	0.308	█████
Confirmed NHS list price (█████ per mg)	█████	0.308	█████
Proposed PAS price (█████ per mg)	£8,818	0.308	£28,626
<b>Refractory to PB/VD alone (4.9% PTH response): Etelcalcetide (with PB/VD) versus cinacalcet (with PB/VD)</b>			
Anticipated list price in CS (█████ per mg)	█████	0.065	█████
Confirmed NHS list price (█████ per mg)	█████	0.065	█████
Proposed PAS price (█████ per mg)	£1,051	0.065	£16,224