Review of TA448; Etelcalcetide for treating secondary hyperparathyroidism

TA448 was published in June 2017 and scheduled to be considered for review in 2020.

Decision

TA448 should be transferred to the 'static' guidance list.

Rationale

We did not identify any new clinical evidence that would change the existing recommendations in TA448. [redacted] or the prices. There is no new evidence to address the uncertainty associated with extrapolating short-term surrogate outcomes to long-term outcomes such as mortality.

Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?

There are no changes to the list price of etelcalcetide. The company confirmed that there are no changes to the existing patient access scheme (simple discount).

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

There are no existing or proposed changes to the marketing authorisation that would affect the existing guidance.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

TA448 recommends etelcalcetide as an option for treating secondary hyperparathyroidism in adults with chronic kidney disease on haemodialysis only if

treatment with a calcimimetic is indicated but cinacalcet is not suitable. This is a narrower population than that covered in its marketing authorisation. The evidence for TA448 was based on 2 placebo-controlled trials, an active-controlled trial comparing etelcalcetide with cinacalcet and a 52-week open-label extension trial. The primary outcome in these trials was the proportion of people with more than a 30% reduction in parathyroid hormone. It is unknown whether a 30% reduction in parathyroid levels translated into directly proportional improvements in long-term outcomes such as survival, cardiovascular events and fractures. The company didn't report long-term data from their trials. The model instead used data from the EVOLVE trial, a large trial that compared cinacalcet with placebo with a follow up period of 64 months, and applied several adjustments to estimate long term outcomes. Therefore, there was uncertainty in establishing the long-term benefits of etelcalcetide compared with cinacalcet. We identified 1 open-label study where the median duration of treatment was 563 days which had the primary outcome measure as the number of participants with adverse events. This study does not address the uncertainty regarding long term benefits so is unlikely to change the recommendation.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

Since publication of TA448 in 2017 there has been no related NICE guidance published that would be relevant to this appraisal.

Additional comments

The search strategy from the original ERG report was adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from July 2016 to August 2020 were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

Equality issues

The committee concluded that no equality issues were identified during the technology appraisal process. No additional equality issues have been identified during the review process.

Proposal paper sign off

Janet Robertson – Associate Director, Centre for Health Technology Evaluation

22 October 2020

Contributors to this paper

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Appendix A – Information from existing guidance

Original remit

To appraise the clinical and cost effectiveness of etelcalcetide within its marketing authorisation for treating secondary hyperparathyroidism in people with chronic kidney disease, receiving haemodialysis.

Current guidance

1.1 Etelcalcetide is recommended as an option for treating secondary hyperparathyroidism in adults with chronic kidney disease on haemodialysis, only if:

- treatment with a calcimimetic is indicated but cinacalcet is not suitable and
- the company provides etelcalcetide with the discount agreed in the patient access scheme.

1.2 This guidance is not intended to affect the position of patients whose treatment with etelcalcetide was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

Research recommendations from original guidance

The committee noted that although the company's incremental cost-effectiveness ratios (ICERs) were below £30,000 per quality-adjusted life year (QALY) gained, these cost-effectiveness estimates are highly uncertain because of uncertainties in extrapolating short-term surrogate outcomes from the etelcalcetide trials to long-term outcomes such as mortality. However, the committee accepted the advantages of having an intravenous calcimimetic option available. Given that there is uncertainty in establishing the long-term benefits of etelcalcetide compared with cinacalcet (for outcomes such as mortality, fracture and cardiovascular events) and higher associated costs, the committee considered that it should be recommended as an option for people with secondary hyperparathyroidism for whom a calcimimetic is indicated, only if cinacalcet is not considered suitable.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred.	NICE will reconsider whether a review is necessary at the specified date.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

Appendix C – Other relevant information

Relevant Institute work

Published

Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy (2007) NICE technology appraisal guidance 117

Review decision: moved to the static list (July 2013)

Hyperparathyroidism (primary): diagnosis, assessment and initial management (2019) NICE guideline NG132

Thyroid disease: assessment and management (2019) NICE guideline NG145

Details of changes to the marketing authorisation for the technology

Marketing authorisation and price considered in original appraisal

Etelcalcetide is indicated for the treatment of secondary hyperparathyroidism in adults with chronic kidney disease on haemodialysis.

NHS list prices:

£136.87 per pack of 6 vials of 2.5 mg in 0.5 ml solution (£9.12 per mg; excluding VAT).

£163.92 per pack of 6 vials of 5 mg in 1 ml solution (£5.46 per mg).

£327.84 per pack of 6 vials of 10 mg in 1 ml solution (£5.46 per mg).

The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of etelcalcetide, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Proposed marketing authorisation (for this appraisal) and current price

No change (current SPC, February 2019)

No change to the list price (BNF, 3 January 2020)

Amgen [redacted] and it is the company's intention to continue with the current patient access scheme in the form of a confidential discount to the list price. Source: letter to NICE (December 2019)

Registered and unpublished trials

Trial name and registration number	Details
Multiple-dose, Double-blind, Double-dummy Study to Compare the Efficacy and Safety of Oral Doses of Cinacalcet Hydrochloride With Intravenous Doses of Etelcalcetide in Asian Hemodialysis Subjects With Secondary Hyperparathyroidism Phase 3 NCT03299244	Purpose: to demonstrate that treatment with etelcalcetide is not inferior to treatment with cinacalcet for lowering serum intact parathyroid hormone (PTH) levels by > 30% from baseline among subjects with chronic kidney disease (CKD) and secondary hyperparathyroidism (SHPT) who require management with hemodialysis. Study design: Quadruple blinding (Participant, Care Provider, Investigator, Outcomes Assessor) Status: completed No. of participants: 637 Start date: May 2018 Study completion: April 2020
Effect of Etelcalcetide on Cardiac Hypertrophy in Hemodialysis Patients: A Randomized Controlled Trial Phase 4 NCT03182699	Purpose: to test the effect of etelcalcetide in comparison to alfacalcidol on left ventricular hypertrophy (LVH) and cardiac fibrosis in hemodialysis patients with secondary hyperparathyroidism Study design: randomised, parallel assignment Status: completed No. of participants: 62 Start date: October 2017 Study completion: December 2019

Trial name and registration number	Details
The Effect of Etelcalcetide on Bone-tissue Properties and Calcification Propensity in End Stage Kidney Disease Phase 2 NCT03960437	Purpose: to test if 9-months of treatment with etelcalcetide improves bone strength in ESKD patients with hyperparathyroidism; and decreases serum propensity to calcify blood vessels. Study design: Single group assignment Status: recruiting No. of participants: 35 Start date: September 2018 Expected completion: June 2021

Additional information

Etelcalcetide (Parsabiv) is not recommended for use within NHS Scotland.

Source: Scottish Medicines Consortium (2017) Etelcalcetide (Parsabiv) SMC ID 1262/17

NHS England (2013) 2013/14 NHS standard contract for specialised endocrinology services (adult)

NHS England (2016) Clinical Commissioning Policy: Cinacalcet for complex primary hyperparathyroidism in adults

References

Block G (2019) An integrated analysis of safety and tolerability of etelcalcetide in patients receiving hemodialysis with secondary hyperparathyroidism. PLOS One 14(3) 1-14