Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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etelcalcetide 2.5mg, 5mg, and 10mg solution for injection (Parsabiv®)

SMC No 1262/17

Amgen Ltd

4 August 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

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

Indication under review: Treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy.

In a phase III study, etelcalcetide was at least as effective as another calcimimetic in reducing parathyroid hormone levels.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by the SMC.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on haemodialysis therapy.[1]

Dosing Information

The recommended initial dose of etelcalcetide is 5mg administered by bolus injection three times per week. Corrected serum calcium should be at or above the lower limit of the normal range before administration of the first dose, a dose increase or re-initiation after a dose stop.

Etelcalcetide should be titrated so that doses are individualised between 2.5mg and 15mg. The dose may be increased in 2.5mg or 5mg increments no more frequently than every four weeks to a maximum dose of 15mg three times per week to achieve the desired parathyroid hormone (PTH) target.

Etelcalcetide is administered into the venous line of the dialysis circuit at the end of the haemodialysis treatment during rinse-back or intravenously (IV) after rinse-back. When given during rinse-back at least 150mL of rinse-back volume should be administered after injection. If rinse-back is completed and etelcalcetide was not administered, then it may be administered IV followed by at least 10mL saline flush volume.

See summary of product characteristics (SPC) for further information.[1]

Product availability date

7 February 2017

Etelcalcetide meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Patients with secondary hyperparathyroidism (HPT) have raised levels of parathyroid hormone (PTH) caused by low serum calcium which leads to excessive release of PTH from the parathyroid gland. Etelcalcetide is a calcimimetic agent which binds to and activates the calcium-sensing receptor on the surface of the parathyroid gland resulting in reduced PTH secretion. The reduction in PTH is also associated with a decrease in serum calcium and phosphate levels.[1]

Etelcalcetide has received marketing authorisation for the treatment of secondary HPT in adult patients with chronic kidney disease (CKD) on haemodialysis therapy. The submitting company has requested that SMC considers etelcalcetide when positioned for use as a treatment option for patients with refractory secondary HPT, i.e. patients with rising serum calcium and uncontrolled PTH levels despite taking phosphate binders and / or vitamin D sterols.

The pivotal study (20120360) was a phase III, multicentre, randomised, active-controlled, double-blind, double-dummy, dose titration study of etelcalcetide compared with cinacalcet in patients with secondary HPT receiving haemodialysis. Adult patients (≥18 years old) with moderate to severe secondary HPT (pre-dialysis serum PTH >500 picograms/mL) who were receiving maintenance haemodialysis three times a week for at least three months were included in the study. Patients were on stable doses of calcium supplements or phosphate binders and vitamin D supplements with corrected serum calcium ≥8.3mg/dL.[2, 3] Eligible patients were randomised equally to receive intravenous (IV) etelcalcetide at an

initial dose of 5mg three times a week plus oral placebo daily (n=340) or oral cinacalcet at an initial dose of 30mg daily plus IV placebo three times a week (n=343) for 26 weeks. Randomisation was stratified according to screening PTH (<900 picograms/mL and >900 picograms/mL) and location (North America or other).[2, 3] Etelcalcetide or IV placebo were administered at the end of the haemodialysis session via a bolus IV injection into the venous line of the dialysis circuit. Dose titrations of study medications aimed to achieve PTH levels of 100 to 300 picograms/mL (investigators were blinded to PTH results) and for etelcalcetide or IV placebo were in increments of 2.5mg or 5mg (range 2.5mg to 15mg) and for cinacalcet or oral placebo in increments of 30mg (range 30mg to 180mg). If a patient had two consecutive PTH values <100 picograms/mL, serum calcium <7.5mg/dL, symptomatic hypocalcaemia, or drug related adverse events the study medicine was withheld.[2]

The primary outcome was the proportion of patients with >30% reduction from baseline in mean pre-dialysis serum PTH level during the efficacy assessment period (weeks 20 to 27) which aimed to demonstrate non-inferiority of etelcalcetide compared with cinacalcet.[2, 3] This was achieved by 58% (198/343) of cinacalcet patients and 68% (232/340) of etelcalcetide patients. The estimated difference between patients in the cinacalcet and etelcalcetide groups in proportions achieving the endpoint was −10% (confidence interval [CI]: −18 to −3.5), p<0.001 for inferiority. Since the upper range of the 95% CI was less than the pre-specified non-inferiority margin of 12%, the non-inferiority criterion was met. The treatment effect was generally consistent across predefined subgroups. [2, 3]

Since non-inferiority was demonstrated for the primary outcome, the following key secondary outcomes were tested sequentially to control for type I error. These included the proportion of patients with >50% reduction in PTH concentrations (tested for superiority) which was achieved by 52% (178/340) of the etelcalcetide group and 40% (138/343) of the cinacalcet group; difference 12% (95% CI: 4.7 to 20), p=0.001;the proportion of patients with >30% reduction in PTH concentrations (i.e. primary outcome tested for superiority): 68% (232/340) and 58% (198/343) respectively; difference of 10% (95% CI: 3.3 to 18), p=0.004 and the mean weekly days of self-reported nausea and vomiting over the first eight weeks which did not differ significantly between treatment groups. The rest of the secondary and exploratory efficacy outcomes generally favoured etelcalcetide over cinacalcet. [2, 3]

Two additional phase III, multicentre, randomised, double-blind studies (20120229 and 20120230) compared etelcalcetide with placebo in patients with secondary HPT receiving haemodialysis. The primary endpoint was the proportion of patients with >30% reduction from baseline in mean PTH during the efficacy assessment period (weeks 20 to 27).[3, 4] In study 20120229 this was achieved by 74% (188/254) of etelcalcetide patients compared with 8.3% (21/254) of placebo patients; difference of 66% (95% CI: 59% to 72%) favouring the etelcalcetide group (p<0.001). Results were similar in study 20120230, 75% of patients (192/255) in the etelcalcetide group compared with 9.6% of patients (25/260) in the placebo group achieved the primary endpoint; difference of 66% (95% CI: 59% to 72%) favouring the etelcalcetide group (p<0.001).[3, 4]

Summary of evidence on comparative safety

In the comparative study (20120360), at least one treatment emergent adverse event was reported in 93% (314/338) of patients in the etelcalcetide group and 90% (307/341) of patients in the cinacalcet group.[5] Serious adverse event rates were similar in both groups, reported by 25% (85/338) of patients in the etelcalcetide group and 27% (93/341) of patients in the cinacalcet group. Adverse events that led to discontinuation of the study treatment occurred in 5.6% (19/338) and 4.7% (16/341) of the etelcalcetide and cinacalcet groups respectively.[3]

The most frequently reported adverse event was decreased calcium levels experienced by 69% (233/338) of patients in the etelcalcetide group and 60% (204/341) of patients in the cinacalcet group.

Decreased calcium levels are a very common adverse effect of etelcalcetide and information is contained within the SPC detailing how to manage this if it occurs.[1]

Nausea was reported by 18% (62/338) of patients in the etelcalcetide group and 23% (77/341) of patients in the cinacalcet group while vomiting was reported by 13% (45/338) and 14% (47/341) of patients in the etelcalcetide and cinacalcet groups respectively.[2]

There were 9 deaths in the etelcalcetide group (2.7%) and 6 deaths in the cinacalcet group (1.8%).[2] These were not considered by the investigator or sponsor to be related to the study treatments.[3]

Summary of clinical effectiveness issues

Chronic kidney disease (CKD) is a common cause of secondary HPT which is a long term progressive condition. Reduced levels of 1,25-dihydroxyvitamin D, hyperphosphataemia, and hypocalcaemia are present in patients with CKD. Patients with secondary HPT have raised levels of PTH caused by low serum calcium which leads to excessive release of PTH from the parathyroid gland.[3, 6] Secondary HPT may lead to pathological bone changes, decreased bone mass, increased risk of fracture, soft-tissue and vascular calcification, left ventricular hypertrophy, increased risk of cardiovascular events and death.[2] Symptoms that patients may also experience include bone and muscle pain and weakness, postural instability, pruritus and neuro-muscular disturbances.[6] Etelcalcetide meets SMC orphan equivalent criteria.

The submitting company has requested that SMC considers etelcalcetide when positioned for use as a treatment option for patients with refractory secondary HPT, i.e. patients with rising serum calcium and uncontrolled PTH levels despite taking phosphate binders and / or vitamin D sterols.

Initially, vitamin D sterols and synthetic analogues can be used to reduce PTH levels in patients with secondary HPT. Phosphate binders may also be used to treat hyperphosphataemia. Parathyroidectomy is an option in patients with uncontrolled secondary HPT. Cinacalcet is an oral calcimimetic licensed for treatment of secondary HPT in patients with CKD receiving dialysis.[2, 3, 6] Within NHS Scotland, cinacalcet is only recommended for patients who have plasma levels of intact PTH >800 picograms/mL that are refractory to standard therapy and a normal or high adjusted serum calcium level and in whom surgical parathyroidectomy is contraindicated.[7]

The pivotal study demonstrated non-inferiority of etelcalcetide compared with cinacalcet relating to the proportion of patients achieving a reduction in mean PTH concentrations of >30% from baseline during weeks 20 to 27. This was supported by superiority in secondary analyses of those achieving >50% and >30% PTH reductions from baseline.[2]

The primary outcome, percentage of patients achieving a >30% reduction in PTH levels, is not a direct health outcome but was considered clinically relevant by the European Medicines Agency (EMA). However, long term outcomes in patients with secondary HPT such as mortality, cardiovascular events and fracture have not been ascertained. The EMA states that it may be difficult to conduct studies with clinical outcomes associated with secondary HPT e.g. fractures or need for parathyroidectomy due to the requirement of a large sample size and long duration.[3]

Inclusion criteria specified that patients were required to have PTH levels of >500 picograms/mL (or >400 picograms/mL in the placebo controlled studies) however this does not confirm that the recruited patients had refractory secondary HPT.[3]

During the efficacy assessment phase (weeks 20 to 27), the median average dose for etelcalcetide was 15mg/week. The maximum licensed dose is 45mg/week. PTH should be measured approximately every one to three months during maintenance treatment with etelcalcetide and dose adjustment may be necessary at any time during treatment including the maintenance phase. There may be uncertainty around whether patients with refractory secondary HPT will require higher doses than those used in the 26 week study period.

The EMA states that due to the lack of robust evidence for the association between PTH levels and risk for mortality, cardiovascular death and fractures there are no specific recommendations for target PTH levels. Guidance produced by the Renal Association and Kidney Disease Improving Global Outcomes (KDIGO) recommends that the target range for PTH for patients on dialysis should be between two and nine times the upper limit of normal.[6, 8] Neither the primary or secondary endpoints in the three studies addressed the patients' PTH levels in relation to these recommendations.

The three key studies had a treatment phase of 26 weeks. This was appropriate for the primary outcome but does not provide long term safety or efficacy data. An open label extension study was conducted where patients were treated with etelcalcetide for up to 52 weeks. This study identified that 68% of patients achieved >30% reduction in PTH. In addition, at month 18 of a second on-going, open label extension study 70% of patients achieved a target PTH of between two and nine times the upper limit of normal, as recommended in clinical guidelines.[9] No new safety findings have been observed in the extension studies.[9, 10]

There are limited patient reported outcomes for etelcalcetide. In the pivotal study, the patient reported secondary outcome of adjusted mean days of self-reported nausea and vomiting per week over the first 8 weeks did not identify any significant differences between groups.[2]

Parathyroidectomy may be carried out, if appropriate, in patients with uncontrolled secondary HPT. There are no available data comparing etelcalcetide with parathyroidectomy.

Clinical experts consulted by SMC considered that the place in therapy of etelcalcetide would be as an alternative to cinacalcet or as a further option for patients who fail to respond to or have poor compliance with cinacalcet. Etelcalcetide is administered at the end of the haemodialysis session and therefore would have minimal service implications other than the time required for the nurse to administer the injection. IV etelcalcetide has the advantage of reducing pill burden compared to daily oral cinacalcet.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of etelcalcetide, as an orphan-equivalent medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Secondary HPT is a serious progressive condition. Patients may experience significant bone pain and are at an increased risk of fractures. Vascular calcification may occur which increases the risk of heart attacks, strokes and peripheral gangrene. High PTH levels can cause resistant anaemia and calciphylaxis. Other symptoms that patients may experience include fatigue, depression, reduced concentration, drowsiness, nausea and loss of appetite.

- Currently the only available options for uncontrolled secondary HPT are oral cinacalcet or parathyroidectomy surgery.

- Clinicians highlighted that patients with CKD receiving dialysis are a high risk patient group for surgery. Parathyroidectomy has known serious complications, even in young otherwise healthy patients and is not practical in frail/older patients. Many patients would prefer to avoid surgery if at all possible.

- Etelcalcetide has been shown to be non-inferior to cinacalcet and, as an IV treatment option, offers advantages of reduced pill burden and improved compliance.

- The potential for improved compliance may also provide reassurance for patients' carers and families.

- Patient groups stressed the importance of patient choice. Patients wish to be able to make an independent and informed decision as to which treatment option is appropriate for them.

Addition of Patient and Carer Involvement

We received a patient group submissions from Kidney Research UK, which is a registered charity. Kidney Research UK has received 7.9% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Kidney research UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost- utility analysis comparing etelcalcetide plus phosphate binders and/or vitamin D sterols to phosphate binders and/or vitamin D sterols alone, for the treatment of patients with refractory secondary HPT ie patients with rising serum calcium and PTH levels despite taking phosphate binders and/or vitamin D sterols. A comparison versus cinacalcet plus phosphate binders and/or vitamin D sterols was also provided and may be considered a relevant comparison as SMC experts have noted that cinacalcet is currently widely used across Scotland.

A Markov model was provided by the company which consisted of three components. The first component (base structure) includes event rates and four clinical outcome health states associated with being off calcimimetic treatment (event free, post fracture, post-CV and post-fracture +CV event). The second and third components incorporate event rates for clinical outcomes depending on the type of calcimimetic treatment received. These components run in parallel to each other ie when a patient receiving etelcalcetide discontinues treatment he/she is assumed to enter the first component of the model and continue to receive only phosphate binders and/or vitamin D sterols. The patients therefore move through the model based on transition probabilities associated with treatment efficacy. The analysis was based on a lifetime horizon of 50 years.

Clinical data used within the economic model were taken from the primary endpoint in key studies ie proportion of patients achieving a >30% reduction in PTH.[2, 4] However, in the economic analysis the company adjusted the treatment effect associated with etelcalcetide and cinacalcet using odds ratios from the placebo controlled studies and the active study. Based on this analysis the proportion of patients achieving the primary endpoint increased in both arms to 66.1% and 75.6% for cinacalcet and etelcalcetide respectively. The company labelled this approach as a 'simple chained indirect comparison'. In order to determine the relative effectiveness of etelcalcetide versus cinacalcet and to estimate the impact of treatment on long term health outcomes, the company adjusted cinacalcet hazard ratios from a long term study using the results from the pivotal studies outlined above.[11] In the base case analysis the company presented results using a lag censored approach which captured events

attributable to treatment for 6 months after patients discontinued. Results were also provided using the ITT population in scenario analyses; however for most clinical outcomes the upper limit of the 95% confidence intervals around the hazard ratios versus cinacalcet was close to 1.

In terms of utility values, a single published study was used to derive these.[12] The utility value for dialysis (0.71) and utility decrements associated with each health state in the model were elicited directly from patients in the long-term cinacalcet study using the EQ-5D questionnaire.[11] Patients in the study were those with moderate to severe secondary hyperparathyroidism and were receiving haemodialysis. Values were adjusted to reflect UK preferences by using time trade off (TTO) responses from 2997 members of the UK public, and a published algorithm.

Medicine costs were included in the analysis. The cost of etelcalcetide, cinacalcet and phosphate binders and vitamin D sterols were calculated based on the weighted average dose per day observed within the pivotal studies. Health state costs were included and were based on a weighted average of elective, non-elective and day case episodes. Monitoring costs were assumed to apply to all secondary HPT patients and included phosphate, calcium and PTH tests. Dialysis costs were not included in the base case analysis and costs associated with adverse events were also not considered.

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The base case incremental cost-effectiveness ratio (ICER) and key sensitivity analyses showing upward uncertainty are presented in the tables below.

Table 1: Base case results (Etelcalcetide PAS price)

Comparator	Incremental costs	Incremental QALYs	Incremental LYs	ICER
Cinacalcet (plus phosphate binders and/or vitamin D sterols)	£679	0.039	0.053	£17,309
Phosphate binders and/or vitamin D sterols	£8,398	0.291	0.397	£28,868

Table 2: Sensitivity analysis (versus phosphate binders and/or vitamin D sterols, Etelcalcetide PAS price)

Parameters	ICER
Base case	£28,868
HR for mortality (upper bound CI)	£51,635
HR for CV (upper bound CI)	£31,678
HR for fracture (upper bound CI)	£30,543
HR for parathyroidectomy (upper bound CI)	£29,057
Etelcalcetide dose increased	£30,400
Dialysis costs included	£62,913

Table 3: Sensitivity analysis (versus cinacalcet plus phosphate binders and/or vitamin D sterols, etelcalcetide PAS price)

Parameters	ICER
Base case	£17,309
HR for mortality (upper bound CI)	£41,907
HR for CV (upper bound CI)	£20,086

HR for fracture (upper bound CI)	£18,594
HR for parathyroidectomy (upper bound CI)	£17,923
Cinacalcet dose reduced	£33,596
Etelcalcetide dose increased	£28,668
Dialysis costs included	£51,226

There were a number of weaknesses including the following;

- The use of the lag censored results in the base analysis may not have been appropriate. Based on discussion with the SMC statistical advisor, the lag censored approach appeared to be a useful means of capturing on treatment efficacy. However, using results from the ITT population may have represented a more appropriate base case. It is worth noting that for the comparison versus cinacalcet, the upper limit of the 95% confidence intervals around the ITT hazard ratios for most clinical outcomes was close to 1. Based on discussion at New Drugs Committee, the committee expressed interest in an analysis whereby these differences were removed. The company subsequently provided analysis, but this only removed the effects in terms of fracture risks; this increased the ICER to £18,355 with PAS.
- There is uncertainty surrounding the clinical data used in the economic model. Due to the lack of direct health outcome data associated with etelcalcetide, the company adjusted long term data from a cinacalcet study using the primary surrogate endpoint from the pivotal etelcalcetide studies to estimate the impact of etelcalcetide on long term health outcomes. Although the EMA considered the surrogate endpoint of the pivotal studies to be clinically relevant and appropriate, the lack of direct health outcome data should be noted as a source of uncertainty and as shown in the sensitivity analysis, the results showed upward uncertainty to using the upper bounds of confidence intervals of the hazard ratios, particularly with respect to survival.
- The base case analysis excluded the costs associated with increased dialysis costs associated with the predicted incremental survival gain versus both comparators in the economic analysis, Sensitivity analysis provided by the company shows that results are sensitive to the inclusion of dialysis costs; inclusion of dialysis costs increased the ICER to £51,226 with PAS.
- The company's approach to estimating the proportion of patients achieving the primary endpoint for etelcalcetide and cinacalcet appears to lack robustness. In the economic analysis, the company adjusted estimates of etelcalcetide and cinacalcet efficacy via a 'simple chained indirect comparison'. Based on this approach, the proportion of patients achieving the primary endpoint was estimated to be 66.1% and 75.6% for cinacalcet and etelcalcetide respectively (as opposed to 57.7% and 68.2% as per the results of the active-control study)[2]. Based on comment from the SMC statistical advisor the approach does not appear to bias the analysis, however it is limited as it assumes transitivity ie similarity between studies. Furthermore uncertainty does not appear to have been addressed as confidence intervals were not provided for point estimates.

The Committee considered the benefits of etelcalctetide in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as etelcalcetide is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept etelcalcetide for use in NHS Scotland.

Additional information: guidelines and protocols

Renal Association guidance: Clinical practice guideline: CKD-mineral and bone disorders (CKD-MBD) published in 2015 recommends that for patients on dialysis (stage 5D) “that the target range for parathyroid hormone measured using an intact PTH assay should be between 2 and 9 times the upper limit of normal for the assay used”. The guidance also recommends that “marked changes in PTH levels in either direction within this range should prompt an initiation or change in therapy to avoid progression to levels outside this range”. In the rationale for these recommendations the Renal Association states that in patients undergoing dialysis the aim to avoid extremes of PTH. Furthermore, the guidance states that “cinacalcet is an extremely effective treatment to control hyperparathyroidism, with reduction in the rate of parathyroidectomies.”[8]

Kidney International / Kidney Disease Improving Global Outcomes (KDIGO) guidance: KDIGO Clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) was published in 2009, with an update scheduled for 2017. The guidance recommends that “in patients with CKD stage 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH.” In addition, the guideline suggests that in patients with CKD stage 5D intact PTH levels should be maintained in the range of approximately two to nine times the upper normal limit for the assay.[6]

These guidelines predate the availability of etelcalcetide.

In line with the NICE (Multiple) Technology Appraisal Guidance No 117 published in January 2007 Healthcare Improvement Scotland advises that the following recommendations for cinacalcet are as valid for Scotland as for England and Wales.

Cinacalcet is not recommended for the routine treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.
However:

Cinacalcet is recommended for the treatment of refractory secondary hyperparathyroidism in patients with end-stage renal disease (including those with calciphylaxis) only in those:

- who have 'very uncontrolled' plasma levels of intact parathyroid hormone (defined as greater than 85 picomol/L [800 picograms/mL]) that are refractory to standard therapy, and a normal or high adjusted serum calcium level, and

- in whom surgical parathyroidectomy is contraindicated, in that the risks of surgery are considered to outweigh the benefits.

Response to treatment should be monitored regularly and treatment should be continued only if a reduction in the plasma levels of intact PTH of 30% or more is seen within 4 months of treatment, including dose escalation as appropriate.[7]

Additional information: comparators

The key comparator is the oral calcimimetic cinacalcet. Patients may also receive vitamin D sterols and synthetic analogues and / or phosphate binders.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Etelcalcetide	2.5mg to 15mg IV three times a week	£3,559 to £12,786
Cinacalcet	30mg to 180mg orally daily	£1,509 to £9,047

Doses are for general comparison and do not imply therapeutic equivalence. IV: intravenously. Costs from MIMS online on 05 May 2017. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 474 patients eligible for treatment with etelcalcetide in year 1 rising to 488 in year 5. The estimated uptake rate was 2% in year 1 (6 patients) and 22% in year 5 (86 patients).

The submitting company requested that the budget impact estimates remain in confidence.

*Other data were also assessed but remain commercially confidential.**

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This assessment is based on data submitted by the applicant company up to and including 16 June 2017.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.