Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

pasireotide (as pamoate), 20mg, 40mg 60mg powder and solvent for suspension for injection (Signifor®) SMC No. (1048/15)

Novartis Pharmaceuticals UK Ltd.

08 May 2015 *(Issued 07 August 2015)*

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 ultra-orphan process

pasireotide (as pamoate) (Signifor®) is accepted for use within NHS Scotland.

Indication under review: Treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue.

Pasireotide administered every four weeks was significantly superior to an active control group (comprising other somatostatin analogues administered monthly) for the primary endpoint of biochemical control, in patients with inadequately controlled acromegaly following treatment with a somatostatin analogue for at least six months.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue.

Dosing Information

Pasireotide (as pamoate) 40mg every four weeks administered by deep intramuscular injection by a trained healthcare professional.

The dose may be increased to a maximum of 60mg for patients whose growth hormone (GH) and/or insulin-like growth factor-1 (IGF-1) levels are not fully controlled after three months of treatment with pasireotide at 40mg. Management of suspected adverse reactions or over-response to treatment (IGF-1 < lower limit of normal) may require temporary dose reduction of pasireotide. The dose may be decreased either temporarily or permanently by 20mg decrements.

The site of repeat intramuscular injections should be alternated between the left and right gluteal muscle.

Product availability date

July 2015
Pasireotide meets SMC ultra orphan criteria in this treatment setting.
Pasireotide has been designated an orphan medicine for the treatment of acromegaly by the European Medicines Agency (EMA).[1]

Summary of evidence on comparative efficacy

Acromegaly is caused by chronic hypersecretion of GH primarily due to GH-secreting pituitary adenoma, and clinical manifestations include progressive somatic disfigurement due to excessive skeletal growth and soft tissue enlargement. In addition, metabolic complications of increased blood glucose levels, hyperinsulinaemia, diabetes, and dyslipidaemia occur. Symptoms such as headache, excessive sweating, arthralgia, paraesthesia and severe lethargy are common. Acromegaly is usually treated with transsphenoidal surgery and effectiveness is variable. In patients who do not achieve normalisation of GH and IGF-1 with surgery or who are not candidates for surgery, additional treatment, usually with medication, will be required. Medical treatments for acromegaly include the use of somatostatin analogues, GH antagonists, and dopamine agonists.[2] Pasireotide is a somatostatin analogue and has activity at four somatostatin receptor subtypes, with higher affinity to subtype 5 and lower affinity to subtype 2 compared to octreotide and lanreotide.[2,3]

Study C2402 (PAOLA) was a phase III randomised parallel-group study in adult patients with inadequately controlled acromegaly, defined as 5-point 2-hour mean GH concentration >2.5 micrograms/L and IGF-1 concentration >1.3 times the sex-adjusted and age-adjusted upper limit of normal. Patients were required to have received continuous monotherapy treatment with octreotide (Sandostatin long-acting release [LAR®]) 30mg or lanreotide (Somatuline Autogel®) 120mg for ≥6 months. If patients had received a GH receptor antagonist or a dopamine agonist,

then these must have been discontinued ≥8 weeks before screening. Previous pituitary surgery was permitted. Patients were randomised equally to monthly injections with pasireotide 40mg, pasireotide 60mg (given every 28 days) or continued treatment with octreotide (Sandostatin LAR®) 30mg or lanreotide (Somatuline Autogel®) 120mg, stratified according to previous treatment (octreotide or lanreotide) and GH concentration at screening (2.5 to 10 micrograms/L or >10 micrograms/L). All were masked to the dose of pasireotide but study drug allocation was open-label. Patients were treated for 24 weeks.[3]

The primary outcome was the proportion of patients achieving biochemical control at 24 weeks, defined as mean GH concentration <2.5 micrograms/L and normalised IGF-1 (between the upper and lower limits of normal) and assessed by a central laboratory. Biochemical control was achieved in 15% (10/65) of patients in the pasireotide 40mg group, 20% (13/65) of patients in the pasireotide 60mg group and no patients in the active control group. The absolute difference for pasireotide 40mg versus control was 15% (95% confidence interval [CI] 7.6 to 26%, p=0.0006) and for pasireotide 60mg versus control was 20% (95% CI 11 to 32%, p<0.0001).[3]

Secondary endpoints included the proportion of patients who achieved IGF-1 normalisation, GH concentration <2.5 micrograms/L and tumour volume reduction of >25% at 24 weeks and are reported in table 1 below.[3]

Table 1: Selected secondary endpoints for study C2402

	Treatment group		
	pasireotide 40mg	**pasireotide 60mg**	**active control**
Number randomised	65	65	68
Proportion of patients achieving normalisation of IGF-1 at 24 weeks			
% (n/N)	25% (16/65)	26% (17/65)	0%
Absolute difference versus active control (95% CI), p-value	25% (95% CI: 15 to 37%), p=0.0006	26% (95% CI: 16 to 38%), p<0.0001	-
Proportion of patients achieving GH concentration <2.5 micrograms/L at 24 weeks			
% (n/N)	35% (23/65)	43% (28/65)	13% (9/68)
Absolute difference versus active control (95% CI) p-value	22% (95% CI: 6.3 to 37%), p=0.0024	30% (95%: CI 13 to 44), p=0.0001	-
Proportion with tumour volume reduction of >25% at 24 weeks			
% (n/N)	18% (12/65)	11% (7/65)	1.5% (1/68)

n=number of patients achieving outcome; N=total number of patients in treatment group CI=confidence interval

Five symptoms of acromegaly (headache, fatigue, perspiration, paraesthesia, and osteoarthralgia) were evaluated every four weeks on a five-point scale from 0 (no symptom) to 4 (very severe). There were improvements from baseline in all groups, with those in the pasireotide groups reaching statistical significance for some symptoms. Health-related quality of life (HRQoL) was assessed every four weeks using the AcroQoL 22-item questionnaire. At week 24 there were numerical improvements in HRQoL from baseline for all groups with statistically significant improvements for the pasireotide 60mg group only.[3]

The extension phase to the study allowed patients in the pasireotide groups who achieved biochemical control at week 24 to continue treatment with pasireotide at the same dose as long as biochemical control was maintained. Patients in the pasireotide groups who did not achieve biochemical control at week 24 could continue on open-label pasireotide 60mg. Patients in the

active control group who did not achieve biochemical control at week 24 were commenced on open-label pasireotide 40mg which could be increased to 60mg should biochemical control not be achieved after three months. At interim analysis (data cut-off; 3 June 2013), 83% of patients included had reached week 28 of the extension phase. The proportion of patients with biochemical control was 22% (9/40) in the pasireotide 40mg group, 42% (15/36) in the pasireotide 60mg group and 21% (10/47) in patients who had crossed over from the active control group.[2]

Summary of evidence on comparative safety

During study C2402, the proportion of patients who reported at least one adverse event was 92% (58/63) in the pasireotide 40mg group, 86% (53/62) in the pasireotide 60mg group and 74% (49/66) in the active control group.[4]

Treatment-related adverse events of any grade (reported in >5% of patients in any group) in the pasireotide 40mg, pasireotide 60mg and active control groups respectively were: hyperglycaemia (33%, 29%, 6.1%), diabetes (19%, 26%, 4.5%), diarrhoea (11%, 19%, 1.5%), cholelithiasis (9.5%, 11%, 12%), increased blood glucose (4.8%, 6.5%, 0%), alopecia (1.6%, 6.5%, 0%), and abdominal pain (6.3%, 4.8%, 0%). Treatment-related grade 3/4 hyperglycaemia occurred in 11% (7/63), 8.1% (5/62) and no patients in the pasireotide 40mg, pasireotide 60mg and active control groups respectively, and treatment-related grade 3/4 diabetes occurred in 3.2% (2/62) of patients in the pasireotide 60mg group only.[3]

A total of six patients discontinued treatment due to adverse events: two patients in the pasireotide 40mg group (one case each of hyperglycaemia and colon cancer) and four patients in the pasireotide 60mg group (one case of diabetes and three cases of hyperglycaemia). All except the colon cancer case were suspected to be treatment related.[3]

Summary of clinical effectiveness issues

Acromegaly is a debilitating condition with a prevalence of 40 to 70 cases per million. Following surgery or when surgery is not appropriate, patients may require medical treatment if they do not achieve normalisation of GH and IGF-1 levels and, first-line, this is usually with somatostatin analogues (octreotide or lanreotide given monthly).[2] The marketing authorisation for pasireotide is for second-line medical use in patients who are not adequately controlled on a somatostatin analogue.[5] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely when surgery and maximum dose somatostatin analogues (with or without dopamine agonists) are unsuccessful and before radiotherapy benefits are seen. Pasireotide meets SMC ultra orphan criteria and has been designated an orphan medicine for the treatment of acromegaly by the EMA[1].

In study C2402, there was a significant difference for both pasireotide groups versus the active control group for the primary outcome of proportion of patients achieving biochemical control (GH concentration <2.5 micrograms/L and normalised IGF-1). Elevated GH and IGF-1 levels are predictors of mortality in patients with acromegaly.[6] However, recently it has been noted that a stricter definition of biochemical response of GH concentration <1 microgram/L and normalised IGF-1 may be more appropriate.[6] In a post-hoc analysis of biochemical response using this

definition, the difference for pasireotide versus active control was statistically significant for the pasireotide 60mg dose only.[2]

The study was conducted in patients who had received octreotide (Sandostatin LAR®) 30mg monthly or lanreotide (Somatuline Autogel®) 120mg monthly for at least six months. In the active control arm, 75% of patients received octreotide 30mg every 28 days. Although in practice the dose of octreotide (Sandostatin LAR®) may be increased to 40mg every 28 days, clinical experts reported that the use of doses exceeding 30mg every 28 days is rare.[7]

The most common adverse events associated with pasireotide treatment were hyperglycaemia, diabetes and diarrhoea. The EMA did not find the benefit-risk balance of pasireotide to be favourable in patients who are naïve to medical treatment due to the high rates of hyperglycaemia and diabetes. Consequently, the approved indication was restricted to patients inadequately controlled with somatostatin analogues.[2]

Although pegvisomant (a GH receptor antagonist) has not been recommended for use by SMC, the submitting company noted that some patients may be treated with it via an individual patient treatment request, which has been confirmed by clinical experts consulted by SMC. Therefore it may be considered a relevant comparator. As there are no direct comparative data, a Bucher fixed effects indirect comparison was conducted to compare pasireotide with pegvisomant monotherapy and in combination with a somatostatin analogue for treatment of inadequately controlled acromegaly. Two pegvisomant studies and study C2402 were included in the analysis. No significant difference between treatments was shown for the outcome of normalisation of IGF-1 levels. There were limitations with the indirect comparison, in terms of heterogeneity of study designs and patient characteristics, and the assumptions made to overcome the issue of no common comparator arm. The only outcome that could be compared was normalisation of IGF-1 levels, as pegvisomant does not have an impact on GH levels, and differing definitions for reduction in tumour volume precluded its analysis. In summary, the results of the indirect comparison should be interpreted with caution. The submitting company noted that no data exist for an appropriate comparison to be made with dopamine agonists.

Clinical experts consulted by SMC considered that pasireotide is a therapeutic advancement as it results in higher rates of biochemical control (compared to other somatostatin analogues), although considered that use would be in a small number of patients.

Pasireotide (as pamoate) requires administration by deep intramuscular injection every four weeks by a trained healthcare professional, compared to octreotide (Sandostatin LAR®) which is administered by deep intramuscular injection every 28 days and lanreotide (Somatuline Autogel®) by deep subcutaneous injection every 28 days.[5,7,8] Administration of pegvisomant requires a loading dose, administered subcutaneously under medical supervision, followed by a once daily subcutaneous injection.[9] The introduction of pasireotide is unlikely to have major service implications.

Summary of patient and clinician engagement

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

The key points expressed by the group were:

- Acromegaly can be a devastating condition, associated with significant morbidity and mortality. If uncontrolled, patients are at greater risk of developing co-morbidities such as cardiovascular disease, diabetes and colon cancer.
- Acromegaly is a challenging condition and impacts the patient both physically and psychologically.
- A small number of patients will be unresponsive to standard treatments and may need multiple treatment options to treat difficult-to-control acromegaly. Pasireotide would give these patients another treatment option when other treatments have failed.
- Radiotherapy can be offered to patients and can be successful but can often take several years to take effect. Pasireotide could be used as a bridging therapy in these patients.
- Clinicians suggested that patients with a sizeable tumour or with tumours adjacent to the optic nerve may particularly benefit from pasireotide.
- Non-responders to pasireotide can be identified within the first few months of therapy; therefore, decisions on stopping treatment in non-responders can be taken early.

Summary of ultra orphan decision-making framework

Pasireotide has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines. Relevant factors under each of the criteria are summarised below.

Nature of the condition
Acromegaly is associated with significant morbidity and premature death. If uncontrolled, patients are at greater risk of developing co-morbidities such as cardiovascular disease, diabetes and colon cancer. Acromegaly also causes symptoms which include: excess growth which can affect internal organs, enlarged lips, nose, feet, hands and tongue, excessive sweating, sleep apnoea, joint pain, headaches, visual loss and extreme fatigue. Acromegaly is a chronic disease with symptoms that are not only disabling but also disfiguring. As a result, the impact on patients' quality of life can be considerable.

Impact of the new technology
The efficacy of pasireotide has been demonstrated in a phase III parallel group study which compared pasireotide to octreotide or lanreotide in patients with **i**nadequately controlled acromegaly. The trial reported a significant difference for pasireotide versus the active control group for the primary outcome of proportion of patients achieving biochemical control.

Pasireotide may also lead to reductions in tumour size. The economic model estimated that the benefits of treatment could translate into a gain in life expectancy of 0.3 years.

As noted above, SMC experts have indicated that there is an unmet need for patients in whom surgery and first line treatment options have not achieved adequate disease control.

Value for Money

The submitting company presented a cost-utility analysis that compared pasireotide against monthly somatostatin analogues (SSA) for the treatment of patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another SSA. The SSA comparator was a weighted average of octreotide and lanreotide.

The company presented a cost-utility analysis to assess the cost-effectiveness of pasireotide against the comparator. A Markov modelling approach was adopted for the analysis as it permitted the transparent and flexible modelling of treatment as well as the observed time delay in responding to radiotherapy.

In terms of model structure, patients entered the model and were treated with pasireotide or SSA. Patient response was assessed after 6 months and those who achieved disease control transitioned to long-term full response where they remained on treatment, or they could optionally switch to second-line treatment. Patients who did not achieve control transitioned to inadequate response where they could remain on treatment or switch to second-line treatment. Second-line treatment in the base case analysis was pegvisomant. Patients who received second-line treatment were also assessed after 6 months and could transition to long-term full response where they remained on treatment, or could transition to inadequate response where they could remain on treatment or switch to radiotherapy. The economic model included a post-radiotherapy state where patients who achieved control following radiotherapy entered a long-term full response health state and were no longer on treatment. Finally, patients could die throughout the model from a number of causes.

The source of the clinical data used in the model for pasireotide, octreotide and lanreotide was the C2402 study. The comparative efficacy of pegvisomant was derived from an indirect comparison. Radiotherapy efficacy data and mortality estimates were taken from published literature.

Baseline utility estimates were calculated using the AcroQOL physical dimension mapping equation from the AcroQOL validation study based on data from the C2402 study. Regression analysis was used to calculate utilities by treatment response (control, inadequate control) and response metric (biochemical control, GH control). The model included disutilities associated with cardiomyopathy, diabetes and hypothyroidism.

Medicines costs were included in the analysis, as were administration costs associated with pasireotide, octreotide, lanreotide and pegvisomant. Other costs in the analysis included the cost of radiotherapy treatment, monitoring costs by treatment response, adverse events and co-morbidity costs.

The base case results indicated that the incremental cost-effectiveness ratio (ICER) for pasireotide versus SSA was £5,855 per quality adjusted life year (QALY) gained. This result was based on an incremental cost of pasireotide versus SSA of £2,141 and an incremental QALY gain of 0.37 QALYs. The company also provided scenario analyses which compared

pasireotide against pegvisomant and pegvisomant+SSA. The results indicated that pasireotide was dominant versus pegvisomant (i.e. more effective and less costly) and less costly than pegvisomant+SSA.

The economic analysis was most sensitive to the SSA probability of biochemical control, patient starting age, co-morbidity costs, pegvisomant medicines costs and pasireotide medicines costs. This was because, when an outer limit of the estimate was used in the analysis, the ICER increased to £125,278, £73,715, £71,837, £67,271 and £52,930 per QALY gained respectively.

The main weaknesses were as follows:

- Patients treated with SSA had a 0% probability of achieving full biochemical control while patients treated with pasireotide had a 15-20% probability of achieving full biochemical control. Therefore, more patients in the economic model who received SSA would have switched to pegvisomant. The results of the analysis were sensitive to the cost of pegvisomant, as when the cost was reduced to £29,200 per year (£36,500 in the base case) the ICER increased to £67,271 per QALY. Also, when pegvisomant was removed from the analysis the ICER increased to £330,789 per QALY. However, this analysis can be considered conservative as SMC clinical experts indicated there was some use of pegvisomant in these patients in practice. In addition, the SMC expert responses also implied that pegvisomant or radiotherapy may be alternative treatment options as opposed to being treated with pegvisomant then moving to radiotherapy.
- The probability of pegvisomant achieving IGF-1 control in the economic analysis was 24%. However, the methodology used to derive this figure was based on an indirect comparison which, as noted above, was associated with a number of limitations. Therefore, although the medicine has an important role in the analysis in terms of influencing the costs of the comparators, the efficacy of the treatment is uncertain. In addition, SMC clinical expert responses have suggested that pegvisomant is effective and a higher probability of response has been used in previous health technology assessments. The company provided an additional sensitivity analysis which increased the efficacy of pegvisomant to 56% and this resulted in an ICER of £28k.
- The economic analysis assumed that patients who achieved full biochemical control at 6 months maintained the treatment effect for as long as they were on treatment. The SMC clinical expert responses have indicated that this is unlikely as the disease tends not to be static and that there is a lack of long term data to support the assumption. The SMC expert responses have also indicated that pasireotide may be used as a bridging or medium term therapy for post-radiotherapy patients until radiotherapy normalises GH hypersecretion. The company response acknowledged that there is no long term evidence regarding the effectiveness of treatment with pasireotide and the company was unable to perform any sensitivity analysis due to substantial technical changes required to the economic model. The company subsequently provided a sensitivity analysis which included a stopping rule for patients who responded to pasireotide, and this resulted in the ICER increasing to £36k. Assuming a decline in treatment effect over time increased the ICER to £19k. Finally, an additional analysis was also provided which reduced the time horizon to 20 years, and this increased the ICER to £32k.
- The economic model was sensitive to treatment response. For example, when the probability of achieving full biochemical control for SSA was increased to 5% (0% in the base case), the ICER increased to £125,278 per QALY. This is because increasing the probability of control for the comparator results in fewer patients moving to second line pegvisomant and therefore the high cost associated with this treatment would be reduced in the comparator arm. In addition, these patients would accumulate other

benefits which would reduce the QALY gain associated with pasireotide. However, it should be noted that the clinical study data appear to support the base case assumption. A related concern was that it was not clear whether full biochemical control was the most appropriate measure for classifying response or whether patients switched treatment because of full biochemical control status. Clinical expert response regarding this issue was mixed but did appear to suggest that full biochemical control was the most appropriate measure of response. The company response indicated that full biochemical control is the primary goal of acromegaly treatment and also referenced that it was the primary clinical endpoint in the C2402 study.

Patient and Clinician Engagement
A Patient and Clinician Engagement (PACE) meeting was held for this submission. Participants at the PACE meeting indicated a range of potential impacts of the new technology for the patient and families/carers.

Impact beyond direct health benefits and on specialist services
At the PACE meeting it was noted that, given the physical and psychological consequences of the disease, many patients find it difficult to maintain their previous routines, social lives or continue in employment. This can impact on quality of life and the finances of patients and their families. The provision of an effective treatment may lessen these impacts.

Costs to NHS and Personal Social Services
The submitting company has estimated that between 8 and 46 patients per year would be treated with pasireotide and that this would be associated with a net drug budget impact of between £132k and £784k per year. The submitting company did not estimate any costs outside of the NHS.

The Committee considered the benefits of pasireotide in the context of the SMC decision modifiers and agreed that the criterion for the potential to bridge to a definitive therapy was satisfied. In addition, as pasireotide is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted pasireotide for use in NHS Scotland.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from The Pituitary Foundation, a registered charity.
- The Pituitary Foundation has received pharmaceutical company funding in the past two years including funding from the submitting company.
- Acromegaly is a debilitating condition that impacts the patient both physically and psychologically. Symptoms can include: fatigue, joint aches, excess growth which can affect internal organs, enlarged lips, nose, feet, hands and tongue, plus protruding lower jaw and brow, excessive sweating, abnormalities of the menstrual cycle, headaches, vision

disturbance, high blood pressure and sleep apnoea. Common co-morbidities including diabetes, valvular heart disease and cardiac dysrhythmias/arrhythmias can severely impact on the quality of life of patients and their families.

- There are very few treatments available for patients suffering from uncontrolled acromegaly and it has an increased mortality rate. Pasireotide would be another treatment option for these patients. Pasireotide may decrease symptoms such as excess growth and enlarged lips, nose, feet, hands and tongue, positively impacting on the patient's quality of life.

- Pasireotide may decrease tumour size more than currently available treatments and as a monthly injection is less burdensome for patients and their carers than most other treatments.

Additional information: guidelines and protocols

The Acromegaly Consensus Group published 'Guidelines for Acromegaly Management: An Update' in 2009.[10] The guidelines recommend transsphenoidal surgery, with complete removal of GH-secreting tumours as the primary treatment choice for patients with acromegaly. Somatostatin analogues are recommended as first-line treatment when the probability of a surgical cure is low; when biochemical control has failed following surgery; as surgical pre-treatment; and disease control (whilst additional therapies such as radiation are underway). Pegvisomant is most appropriate in patients with persisting high IGF-1 levels despite treatment with somatostatin analogues. Dopamine agonists are most appropriate for patients who prefer oral treatment although their efficacy is limited. Radiation therapy is most appropriate for third-line treatment, particularly among patients who do not have tumour growth control or normal hormone levels following surgery and/or medical therapy.

The Acromegaly Consensus Group also published 'A consensus on the medical treatment of acromegaly' in 2014.[6] The guideline notes that surgery remains the primary treatment option and somatostatin analogues are the primary medical treatment option where surgery is not appropriate and after surgery and in patients with a mild disease profile. Dopamine agonists may be considered for use on a short-term basis. In patients with a partial response to somatostatin analogues at optimised doses then pegvisomant may be added and dopamine agonists may also be considered. In patients with no response to a somatostatin analogue then it should be replaced by pegvisomant.

The Endocrine Society/European Society for Endocrinology published 'Acromegaly: An Endocrine Society Clinical Practice Guideline' in 2014.[11] Transsphenoidal surgery is recommended as the primary therapy followed by repeat surgery for patients with residual intrasellar disease. For patients who have not achieved a surgical cure, then primary adjuvant therapy with somatostatin analogues or pegvisomant is suggested for patients with moderate to severe disease characteristics and a dopamine agonist in patients with a modest disease profile. In patients who have an insufficient response to somatostatin analogues then pegvisomant or dopamine agonist therapy is recommended. Radiotherapy is recommended for patients with residual tumour following surgery, in cases where medical treatment is not possible, unsuccessful or not tolerated.

These guidelines predate the availability of pasireotide.

Additional information: comparators

Somatostatin analogues (given monthly), pegvisomant (not recommended for use by SMC).

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Pasireotide (as pamoate)	**40mg to 60mg by deep intramuscular injection every 28 days.**	**29,900**
Pegvisomant	10mg to 30mg by subcutaneous injection once daily (following a loading dose of 80mg)*.	18,200 to 54,600
Octreotide (Sandostatin LAR®)	20mg to 40mg by deep intramuscular injection every 28 days.	10,089 to 16,197
Lanreotide (Somatuline Autogel®)	60mg to 120mg by deep subcutaneous injection every 28 days.	7,163 to 12,181

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eMIMs on 21.1.15.*excludes cost of 80mg loading dose. Pegvisomant has not been recommended for use by SMC.

Additional information: budget impact

The submitting company estimated there to be 76 patients eligible for treatment with pasireotide in year 1, and 91 patients in year 5. Treatment uptake was estimated at 10% in year 1, rising to 50% in year 5. This resulted in 8 patients assumed to be treated in year 1, rising to 46 patients in year 5.

The submitting company estimated the gross medicines budget impact to be £229k in year 1 and £1.4m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £132k in year 1 and £784k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. European Medicines Agency. Public summary of positive opinion for orphan designation of pasireotide for the treatment of acromegaly (EMEA/COMP/454500/2009). 13 October 2009. www.ema.europa.eu
2. European Medicines Agency. European Public Assessment Report for pasireotide (Signifor®). EMA/CHMP/524716/2014 25 September 2014. www.ema.europa.eu
3. Gadelha M, Bronstein M, Brue T et al. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. Lancet Diabetes Endocrinology 2014.
4. Colao A BM, Brue T, Coculescu M et al. Phase III, multicenter, randomized study (PAOLA) demonstrating that pasireotide LAR has superior efficacy over octreotide LAR and lanreotide Autogel in patients with inadequately controlled acromegaly. In: ENDO. Chicago, IL, USA. 2014.
5. Pasireotide powder and solvent for suspension for injection (Signifor®). Summary of product characteristics. Novartis Europharm Limited. European Medicines Agency www.ema.europa.eu. Last accessed 15 January 2015.
6. Giustina A, Chanson P, Kleinberg D et al. Expert consensus document: A consensus on the medical treatment of acromegaly. Nature reviews. Endocrinology 2014; 10: 243-8.
7. Octreotide (Sandostatin® LAR) powder and solvent for suspension for injection. Summary of product characteristics. Novartis Pharmaceuticals UK Ltd. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 3 December 2014.
8. Lanreotide (Somatuline Autogel®) powder for suspension for injection. Summary of product characteristics. Ipsen Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 4 November 2014.
9. Pegvisomant (Somavert®) powder and solvent for solution for injection. Summary of product characteristics. Pfizer Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated February 2014.
10. Melmed, S., Colao, A., Barkan, M., et al. Guidelines for Acromegaly Management: An Update. Journal of Clinical Endocrinology and Metabolism. 2009; 94(5), 1509-1517.
11. Katznelson, L., Laws, E.R., Melmed, S et al. Acromegaly: An Endocrine Society Practice Guideline. Journal of Clinical Endocrinology and Metabolism. 2014: 99(11), 3933-3951.

This assessment is based on data submitted by the applicant company up to and including 13 March 2015.

Drug 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.

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.