Evidence Review:

Pasireotide for acromegaly as third-line treatment (adults)

NHS England

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1. Introduction

Acromegaly is a rare, seriously debilitating condition that usually develops over many years, characterised by excessive secretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). In the vast majority of patients (>99%), it is caused by a GH-secreting pituitary adenoma. Acromegaly is associated with a two to three fold increase in mortality. Factors contributing to increased mortality include higher prevalence of hypertension, hyperglycaemia or diabetes, cardiovascular disease, cardiomyopathy and sleep apnoea.

The clinical manifestations of acromegaly are due to the peripheral actions of the GH excess and elevated IGF-1 concentrations and/or local tumour mass effect. The symptoms and signs of acromegaly can be divided into physical (changes due to excessive amounts of GH and IGF-1), metabolic (effects of excessive amounts of GH) and local (effects of the pituitary tumour).

The therapeutic goals are to reduce mortality to the expected age- and sex-adjusted rates by using treatments that either remove the tumour mass or control its growth and restore GH secretion and action to normal. The biochemical goals are to reduce the circulating IGF-1 levels to normal for age and sex and to reduce serum GH concentrations to < 1 µg/L. The epidemiological data available suggest that reduction of GH to this level or normalisation of IGF-1 improves the standardised mortality rate of acromegalic patients to close to that of the general population. However, despite all the different therapeutic approaches available, several real world studies suggest that a substantial number of patients do not achieve optimal biochemical control.

Pasireotide is a long-acting release somatostatin analogue, licensed in the UK for use in the treatment of adult patients when surgery has failed (or is not an option) and who are inadequately controlled with another somatostatin analogue (SSA) (octreotide/lanreotide).

2. Summary of results

To note, all the trials to date were funded by Novartis Pharm AG. Earlier trials adopted a composite endpoint of Growth Hormone (GH) <2.5 µg/l and normalised Insulin-like Growth Factor (IGF-1); more recently this has been changed to achieving GH <1 µg/l, to align with revised Endocrine Society guidelines.

1. Is Pasireotide a clinically effective treatment in adults with acromegaly when surgery has failed (or is not an option) and who remain inadequately controlled with another somatostatin analogue?

Gadelha et al (2014) (level-1) in the PAOLA phase three trial (n=198) evaluated the clinical effectiveness of Pasireotide LAR at two doses (40mg/monthly (n=65) and 60mg/monthly (n=65)) in patients with acromegaly who were previously inadequately controlled (GH>2.5µg/l and IGF-1 > 1.3 times the upper limit of normal (ULN)), on either 30mg Octreotide LAR or 120mg Lanreotide monotherapy. 132 of 198 patients had undergone previous surgery. 68 patients continued on their current therapy as an active control group. At 24 weeks 15% of patients in the Pasireotide 40mg group, 26% in the 60mg group and 0% in control group achieved primary endpoint (normalisation of IGF-1 and GH<2.5µg/l). Normalisation of IGF-1 was achieved in 25% of patients in the Pasireotide LAR 40mg group, 26% in the 60mg group and none in the active group. In addition tumour reduction >25% was observed in 18.5% of patients in the Pasireotide 40mg group and 10.8% in 60mg group and one patient in the control group. The study concluded that Pasireotide LAR had superior efficacy in patients that were inadequately controlled, compared to Octreotide and Lanreotide. The absolute difference in the control group for 40mg of Pasireotide was 15.4% (p=0.0006) and 20% in the 60mg group p<0.0001.

However, Gadelha et al (2014) also observed the higher incidence of hyperglycaemia adverse events: 33% (n=21) in the 40mg Pasireotide group, 31% (n=19) in 60mg group and 14% (n=3) in the active control group. At baseline assessment, 72% in the 40mg group, 60% in 60mg and 69% in the active control group had diabetes (n=35). An increase in fasting blood glucose levels was observed at all doses (dose of Pasireotide LAR 20, 40 and 60mg), and greatest in the 60mg. Associated reduction in fasting insulin levels and an increase in hbA1c was observed in all patients. 11% of patients in this study experienced a hyperglycaemia related adverse event. The European Medicine Agency has provided clinical guidance and recommended careful monitoring of glycaemic status prior to and during Pasireotide treatment and to manage hyperglycaemia with pharmacotherapy (www.ema.europa.eu/ema).

Petersenn et al (2014) (level 2++) in a randomised multi-centre open label phase I study (n=35) assessed pharmacokinetics, pharmacodynamics and safety of Pasireotide LAR at three doses 20mg, 40mg and 60mg. 34 of the 35 acromegalic patients with a pituitary adenoma had previously received somatostatin analogues but failed to gain biochemical control. Assessment at day 91 following Pasireotide showed GH and IGF-1 levels had decreased in all patients. 51% of patients had a mean GH level <2.5 µg/l, and 57% a mean IGF-1 level below the upper limit of normal.

Similarly Marina et al (2015) (level 3) reported two patients that failed to achieve achieved biochemical and symptomatic control following surgery and treatment with Octreotide LAR. Following Pasireotide treatment both patients achieved control and symptomatically improved. One patient discontinued treatment after 7 months, as result of hyperglycaemia, with increasing fasting glucose and Hba1c above the reference range.

In summary, the PAOLA trial (level -1), short-term (24 weeks) powered, randomised non-blinded study concluded that Pasireotide can be an effective treatment for adults with acromegaly who remain inadequately controlled with another somatostatin analogue. In this study 67% of patients had undergone previous surgery. Larger multicentre long-term, double blinded randomised trials, with stratification of the patient group would strengthen this evidence base.

2. Is Pasireotide more effective than the comparison therapies (listed above) in achieving the critical and important patient outcomes as detailed above?

Colao et al (2014) (level +1) in a large multicentre double blinded randomised trial (n=358 patients), found Pasireotide LAR at 12 months, to have shown superior efficacy in achieving biochemical control when compared to Octerotide LAR (31.3% vs 19.2% respectively, P=0.007), in medically naïve acromegaly patients. Patients were stratified on further analysis as de novo or post-surgical. Normal IGF-1 level, were achieved in 50.7% of post-surgical patients in the Pasireotide group compared to 26.9% in the Octreotide group. Normalisation of IGF-1 levels was achieved in 35% of de novo patients in the Pasireotide group versus 21.2% in Octreotide group. Overall both treatments showed similar reduction in tumour mass from baseline 40% in Pasireotide LAR and 38% in Octreotide LAR (P=0.838), and both drugs were similarly effective at improving symptoms and quality of life.
An extension phase of the study (Sheppard et al (2015) (level 1-)) evaluated 120 patients with acromegaly who had GH<2.5µg/l and IGF-1≤1xULN at 12 months and/or experienced clinical benefit. 74 patients in the Pasireotide LAR and 46 patients in the Octreotide LAR group continued with the extension phase. The study found GH and IGF-1 suppression was maintained up to 25 months, 48.6% patients in Pasireotide LAR group and 45.7% (n=21) in Octreotide LAR group achieved primary endpoint.

Colao et al (2014) also found hyperglycaemia related adverse events were more common in the Pasireotide LAR group (57.3% versus 21.7% in the Octreotide group). Sheppard et al (2015) (level 1-) in the extension phase study found the safety profile of Pasireotide LAR to be similar to Octreotide LAR, except the increase in hyperglycaemia related events in the Pasireotide group. The majority of patients experienced one mild/moderate adverse event (86.5% in Pasireotide group versus 77.2% in Octreotide LAR group). Common side effects included diarrhoea and cholelithiasis.
To date, one double blinded randomised study and extension phase of the study shown that Pasireotide can be more effective than comparison therapies.

3. Is Pasireotide a cost effective treatment in patients with adults with acromegaly when surgery has failed (or is not an option) and who remain inadequately controlled with another somatostatin analogue?

No studies have evaluated cost effectiveness of Pasireotide treatment in acromegaly patients when surgery has failed (or is not an option) and who remain inadequately controlled with another somatostatin analogue.

4. Is Pasireotide more cost effective than comparison therapies (listed above)?

No studies have evaluated cost effectiveness of Pasireotide treatment when compared to other therapies.

3. Research questions

1. Is pasireotide a clinically effective treatment in adults with acromegaly when surgery has failed (or is not an option) and who remain inadequately controlled with another somatostatin analogue?
2. Is pasireotide more effective than the comparison therapies (listed above) in achieving the critical and important patient outcomes as detailed above?
3. Is pasireotide a cost effective treatment in patients with adults with acromegaly when surgery has failed (or is not an option) and who remain inadequately controlled with another somatostatin analogue?
4. Is pasireotide more cost effective than comparison therapies (listed above)?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
2++	RCT	35 patients	Patients randomised 1:1:1 to receive pasireotide LAR monthly at a dose of i) 20mg/month ii) 40mg/month or iii) 60mg/mg. Patients received three monthly injection. Pasireotide naïve patients received a single test dose of 300µg subcutaneously followed by a minimum 5 day washout.	Safety of the interventio n	To investigate the safety/ tolerability and pharmacokin etic profile of single and monthly doses of pasireotide LAR20,40 and 60mg	i) Pharmacokinetic profile: Steady state pasireotide concentrations were observed following three monthly injections and were almost dose proportional. Mean and median trough concentrations following the first injection were approximately 70-90% of trough levels at steady state for all three doses. Accumulation ratio was approximately 1.0 across all groups, suggesting minimal drug accumulation. ii) Safety: Refer to adverse events category. iii) Glucose homeostasis: Fasting blood glucose (FBG) levels increased with all doses from baseline, greatest increase in the 60mg group, with an associated reduction in fasting insulin levels in all doses of pasireotide LAR. Also an increase in HbA1c was observed in all treatment groups from baseline.	Asses pharmacodyn amics. Symptoms of acromegaly (headache, perspiration, paraesthesia, fatigue and osteoarthralgi a) were reported at baseline, days 35, 63 and 91 using a five point severity scale (0=absent, 1=mild, 2=moderate, 3=severe and 4=very severe)	i) Biochemical parameters: GH and IGF-I: GH levels decreased in all patients. By day 91 51% of patients had mean GH levels ≤2.5µg/L. The mean percentage decrease from baseline to D91 in the pasireotide LAR 20, 40 and 60mg group were as follows -66.8%, -59.7% and -63.2%. Mean IGF-1 decreased after injection in all treatment groups. At day 91 57% of patients had serum IGF-1 level below the upper limit of the normal range. The mean percentage decrease in pasireotide LAR 20, 40 and 60mg groups were -40.2%, -50.7% and -49.8% respectively. ii)Symptoms: Compared to baseline patients reported less acromegaly related symptoms. At baseline 21/35 patients reported headaches, 30/35 perspiration, 22/35 paraesthesia, 31/35 fatigue and 30/35 osteoarthralgia. At day 91 according to the five point scale symptoms had improved in 16/21, 23/30. 15/22. 16/31 and 17/30 patients respectively.	Petersenn, Stephan; Bollerslev, Jens; Arafat, Ayman M.; Schopohl, Jochen; Serri, Omar; Katznelson, Laurence; Lasher, Janet; Hughes, Gareth; Hu, Ke; Shen, George; Reséndiz, Karina Hermosillo; Giannone, Vanessa; Beckers, Albert. Pharmacokinetics, pharmacodynamics, and safety of pasireotide LAR in patients with acromegaly: a randomized, multicenter, open-label, phase I study. J Clin Pharmacol 2014;54(11):1308-1317.	Safety evaluated as primary outcome. 24 out of 35 patients experienced at least one adverse event, which were predominately mild, 34.3% reporting diarrhoea and 14.3% nasopharyngitis. 11 patients (31%) experienced hyperglycaemia related adverse events, 2 in 20mg group, 2 in 40mg and 6 in 60mg group. two patients in the 60mg group were hospitalised, one patient for exacerbation of diabetes mellitus and other renal colic. No deaths were reported.	Yes	Randomised open label phase I trial. Small study lacking power and not blinded, with a lack of control group for comparison. Study downgraded to 2++ Population characteristics Adults patients with confirmed diagnosis of acromegaly, with a pituitary adenoma were eligible. Acromegaly confirmed by elevated circulating IGF-1 and GH levels ≥1µg/l following an oral glucose tolerance test (OGTT). Patients previously treated with pasireotide subcutaneously were eligible. Patients were excluded if they had tumour compression of the optic chiasm resulting in visual defect, surgical intervention for symptoms result of a mass effect, major surgical procedure within 1 month or radiotherapy within 2 years. Excluded if uncontrolled type 2 diabetes mellitus, symptomatic cholelithiasis, abnormal coagulation, clinically significant heart disease or liver disease. 23 males and 12 females were randomised. 34 patients had previously received somatostatin analogues, 8 patients pasireotide SC. Baseline serum IGF-1 obtained for all patients, GH profiles in 8/10, 11/12 and 8/13 patients in the pasireotide LAR 20, 40 and 60mg group.

1-	RCT	198 patients	Patients randomised 1:1:1 to receive 40mg Pasireotide LAR (n=65) once every 28 days or 60mg pasireotide LAR (n=65) every 28 days	Clinical effectiveness of the intervention compared to existing interventions	To assess the number of patients achieving biochemical control, growth hormone <2.5µg/l and normalisation of IGF-1 concentration.	At 24 weeks 15% (n=10) of patients in the pasireotide 40mg group and 20% (n=13) in the 60mg group achieved biochemical control. No patient in the active control group achieved control. The absolute difference from control group for 40mg pasireotide group was 15.4% (95% CI 7.6-26.5) p=0.0006 and 60mg group 20% (CI 11.1-31.8) p<0.0001.	To assess i) proportion of patients achieving normalised IGF-1 concentration at 24 weeks. ii) Proportion of patients achieving 5-point 2hr mean GH conc <2.5µg/l iii) tumour reduction of >25% iv) health related quality of life questionnaire	i) At 24 weeks IGF-1 normalisation was achieved in 25% (n=16) patients receiving pasireotide LAR 40mg, 26% (n=17) in the 60mg group and in no patients in the active control group. Mean IGF-1 values decreased from baseline to week 12 and remained stable until week 24 in both pasireotide group. Mean percentage change in IGF-1 values at week 24 was -28%, in the 40mg group, -38.6% 60mg group and -7.2% in the active group. ii) Mean GH conc< <2.5µg/l at week 24 was achieved in 35% (n=23) in the pasireotide LAR 40mg group, 43% (n=28) in the 60mg group and 13% (n=9) in the active control group. Mean percentage change in GH conc between baseline and week 24 were -23.1% in the 40mg group, -50.9% in 60mg and -3.2% in the active control group. iii) tumour reduction >25% was observed in 18.5% (n=12) 40m group, 10.8% (n=7) in 60mg group and in one patient in the active control group. iv) Patients in all groups had overall improvement of QoL score, although observed patients in the pasireotide groups had greater improvement when compared to the active control group.	Gadelha, Mônica R.; Bronstein, Marcello D.; Brue, Thierry; Coculescu, Mihail; Fleseriu, Maria; Guitelman, Mirtha; Pronin, Vyacheslav; Raverot, Gérald; Shimon, Ilan; Lievre, Kayo Kodama; Fleck, Juergen; Aout, Mounir; Pedroncelli, Alberto M.; Colao, Annamaria; Pasireotide C2402 Study Group. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. Lancet Diabetes Endocrinol 2014;2(11):875-884.	6 patients discontinued treatment because of adverse events, 2patients in 40mg pasireotide group and 4 patients in the 60mg group. Common adverse events were hyperglycaemia (33% (n=21) treatment with 40mg pasireotide, 31% (n=19) with 60mg pasireotide, 14%(n=3) with active control). Diabetes in 21% (n=13) in 40mg group, 26% (n=16) 60m group and 8% (n=5) in control group. Diarrhoea in 16%(n=10), 19%(n=12) and 5%(n=3) respectively. Serious adverse events reported in 10% (n=6) in 40mg group, 3%(n=2) in 60mg and 5%(n=3) in active control group	Yes	Authors conclude that pasireotide LAR was shown to have superior efficacy in achieving biochemical control when compared with continued treatment with octreotide or lanreotide (first generation somatostatin analogues). No patients in the active control group achieved biochemical control or normalised IGF-1 concentrations. Multicentre (51 centres in 18 countries) randomised parallel group phase 3 trial. 62 patients per treatment group was estimated to achieve 90% power to detect a difference of 20% in response rate between active control and pasireotide LAR groups. Patients and study investigators blinded towards dose of pasireotide although not towards the drug that was assigned. As a result of lack of blinding, study downgraded Population characteristics Adults patients with acromegaly that were inadequately controlled (5-point, 2hr mean GH>2.5µg/l and IGF-1>1.3 times the upper limit of normal (ULN), and had received 30mg of octreotide long acting or 120mg lanreotide as monotherapy for at least 6 months. Patients that were on concomitant therapy with a growth hormone antagonists or dopamine agonist were eligible, although required the drugs to be discontinued for at least 8 weeks prior to enrolment. Patients were stratified according to previous treatment and growth hormone concentrations at screening (2.5-10µg/l and > 10µg/l). 132 of 198 patients had received surgery previously. 72% of patients in the 40mg group, 60% in 60mg and 69% in active control group had diabetes at baseline.

1+	RCT	358 patients	176 Patients randomised to receive pasireotide LAR 40mg every 28 days. At 3 and 7 months titration to 60mg was permitted.	Clinical effectiveness of the intervention compared to existing interventions	To assess the proportion of patients that have achieved biochemical control GH<2.5µg/l and normalisation of IGF-1 concentration	Overall 80.1% of pasireotide LAR and 85.7% of octreotide LAR patients completed 12 months of treatment. At 12 months biochemical control was achieved significantly more in the pasireotide LAR patients than octreotide patients, 31.3% vs 19.2% respectively, P=0.007. During the 12 months 50.6% of pasireotide LAR and 67.6% of octreotide LAR patients received an increase in dose titration. 31% of patients in the pasireotide group and 22.2% in the octreotide group did not achieve biochemical normalisation and did not receive dose increase.	To assess i) proportion of patients achieving normalised IGF-1 concentration at 12 months ii) Proportion of patients achieving GH conc <2.5µg/l iii) decrease in tumour volume iv) change in signs, symptoms and health related quality of life (HRQoL).	i) In pasireotide LAR and octreotide LAR group respectively 38.6% and 23.6% (P=0.002) achieved normal IGF-1. Normal IGF-1 was achieved in 50.7% of post surgical patients in the pasireotide group compared to 26.9% in the octreotide group. De novo patients 30.5% versus 21.2% respectively. ii) GH levels <2.5µg/l was achieved in in 48.3% of patients in the pasireotide LAR group and 51.6% in the octreotide patients, P=0.58. iii) mean tumour volume reduced in both groups from baseline to 12months, 40% pasireotide LAR and 38% in octreotide LAR (P=0.838). iv) Both drugs were similarly effective at improving symptoms and QoL.	Breitschaft, Astrid; Hu, Ke; Hermosillo Reséndiz, Karina; Darstein, Christelle; Golor, Georg. Management of hyperglycemia associated with pasireotide (SOM230): healthy volunteer study. Diabetes Res. Clin. Pract. 2014;103(3):458-465.	8% of patients in pasireotide LAR and 3.3% in the octreotide LAR group discontinued therapy as result of adverse events, commonest reason for discontinuation in the pasireotide group was related to blood glucose . Hyperglycaemia related adverse events were more common with pasireotide LAR (57.3% vs 21.7%). Most common AE in both groups were mostly mild to moderate, diarrhoea in 39.3% in the pasireotide group vs 45% in octreotide group, cholelithiasis 25.8% vs 35.6%, headaches 18.5%vs25.6% and hyperglycaemia 28.7% vs 8.3% respectively.	Yes	Prospective randomised double blinded study at 84 sites in 27 countries. Authors conclude that pasireotide LAR was shown to have superior efficacy in achieving biochemical control when compared with octreotide LAR. Population characteristics Adults patients with acromegaly naïve to medical treatment. Patients with GH>5µg/l or GH nadir≥1µg/l after an OGTT and IGF-1 above the ULN. Patients were stratified into two groups, firstly those that had undergone pituitary surgery, and secondly de novo patients with a pituitary adenoma evident on MRI imaging and refused surgery or in whom surgery was contraindicated. The two groups were similar in terms of baseline demographics, 58% patients were de novo. In the pasireotide LAR and octreotide LAR groups the baseline mean GH was 21.9 and 18.8µg/l, and mean standardised IGF-1 was 3.1 and 3.1 times the ULN and baseline mean tumour volume was 2421 and 2259mm2 respectively. Patients were excluded if previously received medical treatment (somatostatin analogs, dopamine agonists or GH receptor antagonists), compression of optic chiasm, surgical intervention required for relief of symptoms related to tumour compression, pituitary irradiation within the last 10 years, significant cardiovascular morbidity and/or liver disease, symptomatic cholelithiasis and a HbA1c>8%.

1-	RCT	120 patients	120 patients that completed the core study, 74 patients continued with pasireotide LAR and 46 patients with octreotide LAR in the extension study. Patients continued with the dose from the initial study and dose was reviewed in the extension phase and if not achieving biochemical control an opportunity to increase to a maximum of 60mg pasireotide LAR every 28 days and 30mg octreotide LAR every 28 days.	Clinical effectiveness of the intervention compared to existing interventions	To assess the efficacy and safety in the pasireotide LAR and octreotide LAR groups for up to 26 months. To assess biochemical control (GH<2.5µg/l and normal IGF-1)	Patients that continued in the extension phase at entry point 71.6% in the pasireotide LAR and 56.5% in the octreotide LAR arm had GH<2.5 µg/L and IGF-1 ≤1xULN, and after 25 months this was 60.8% and 52.2% respectively. 48.6% patients (n=36) in pasireotide LAR group and 45.7% (n=21) in octreotide LAR group achieved biochemical control at 25 months.	To assess i)tumour volume reduction ≥20% from baseline to month 26 and ii) effects on signs and symptoms of acromegaly	At month 26 74.7% patients in pasireotide LAR and 71.6% in octreotide LAR group exhibited a >20% reduction in tumour volume. The mean decrease in the pasireotide LAR group was 600±735mm3 (51.8% decrease) and octreotide LAR group 1120±2541mm3 (55% decrease). ii) In both groups the five assessed symptoms (headache, fatigue, perspiration, osteoarthralgia and paraesthesia) all improved.	Petersenn, S.; Schopohl, J.; Barkan, A.; Mohideen, P.; Colao, A.; Abs, R.; Buchelt, A.; Ho, Y.-Y.; Hu, K.; Farrall, A. J.; Melmed, S.; Biller, B. M. K.; Pasireotide Acromegaly Study Group. Pasireotide (SOM230) demonstrates efficacy and safety in patients with acromegaly: a randomized, multicenter, phase II trial. J. Clin. Endocrinol. Metab. 2010;95(6):2781-2789.	Overall 31.1% of patients in the pasireotide LAR group and 21.7% patients in the octreotide LAR group discontinued treatment, majority withdrew consent as were undergoing pituitary surgery. 2.7% of patients (n=2) in the pasireotide and 2.2% (n=1) in octreotide discontinued because of adverse events. The majority of adverse events were mild or moderate, and most patients during the 26 months reported at lease one AE (86.5% in pasireotide and 77.2% in octreotide LAR group). Most common AEs were diarrhoea and cholelithiasis. Hyperglycaemia related events were observed in 62.9% of patients in the pasireotide LAR and 25% in the octreotide LAR group. In the 25 months at least 50% of the patients in the pasireotide group was receiving an anti-diabetic medication, commonly metformin to achieve glucose homeostasis.	Yes	Authors concluded GH and IGF-1 suppression is maintained up to 25 months during pasireotide LAR treatment and with a safety profile typical of other somatostatin analogue, except an increase frequency of hyperglycaemia related events. Large randomised double blinded phase III study extension study. Extension phase of the study included patients with acromegaly from the Colao et al study (2014), patients were naive to medical treatment and randomised to pasireotide LAR or octreotide LAR every 28 days for 12 months. Fewer patients in the octreotide LAR group were eligible to continue which reflects the results from the Colao study, hence unequal proportion of patients in the extension phase of the study. It is not clear whether the extension phase was appropriately powered. Study level downgraded. Population characteristics 120 patients with acromegaly that had GH<2.5µg/l and IGF-1 ≤1xULN at month 12s or patients experiencing clinical benefit were eligible to continue receiving randomised therapy in the extension. Included patients with acromegaly from the Colao et al study (2014), patients were naive to medical treatment and randomised to pasireotide LAR or octreotide LAR every 28 days for 12 months. Of the 141 patients in the pasireotide LAR group that completed the 12 month study, 74 patients continued with the blinded extension study. 156 patients in the octreotide completed 12months and 46 patients continue with the extension phase.

3	case report	2 patients	Pasireotide LAR treatment following treatment with octreotide (both short and long acting)	Clinical effectiveness of the intervention	Assessment of headache (symptoms of acromegaly) and biochemical control	Case 1: Following surgery and octreotide (short/long acting) and pegvisomant commenced on pasireotide LAR, that resulted after the first infusion symptomatic relief of headaches. Also whilst on treatment GH decreased and IGF-1 normalised and the tumour remnant size remained stable. After 2 years of pasireotide treatment dose was increased in response to a rising IGF-1. Case 2: Patient initially received 3 doses of pasireotide at 40mg/month and then on 4 occasions 60mg/month. Treatment results in normalisation of IGF1 levels and regression of acromegaly symptoms. At 7 months treatment discontinued and patient underwent stereotactic gamma knife radiation for tumour remnant resulting in normalisation of IGF-1	0	0	Colao, Annamaria; Auriemma, Renata S.; Pivonello, Rosario. The effects of somatostatin analogue therapy on pituitary tumor volume in patients with acromegaly. Pituitary 2015;0(0):0.	Case 2: patient discontinued therapy after 7 months as a result of hyperglycaemia, an increase in fasting glucose and HbA1c to above the reference ranges.	Yes	A low level evidence study. Population characteristics 2 acromegalic patients with severe headaches and biochemical disturbances (initially high GH and IGF1 concentrations). Case 1: 21 year old women with severe headaches and initially high GH and IGF1 concentration, MRI showed evidence of pituitary macroadenoma, and patient underwent surgery. Persistence of disease led to a second debulking surgery with resection of 80% of tumour mass. Patient continued to be symptomatic and unable to achieve biochemical control, and commenced on short acting octreotide and then long acting and pegvisomant. Surgical specimens of the tumour from the first surgery revealed at the membranous level tumour cell expression of >75% of sst2a and 90% of sst5. Specimens from second surgery ssta2 expressed in 50% and sst5 in 100% of tumour cells. Case 2: 33 year old woman presented with 4 year history of headaches and with elevated GH/IGF-1 levels and on MRI pituitary macroadenoma was evident, and diagnosed with acromegaly. In addition had symptoms such as perspiration, weight gain, tiredness, oligomenorrhea and mild hirsutism. Patient initially treated with octreotide with resolution of symptoms but persistent biochemical abnormality. Patients subsequently underwent two surgeries in attempt to achieve control. Evaluation of tissues from second surgery ssta2 expressed in 50% and ssta5 >75% of tumour cells.
-	other	-	-	-	-	-	-	-	McKeage, Kate. Pasireotide in Acromegaly: A Review. Drugs 2015;75(9):1039-1048.	-	-	Review article only, referenced in CER summary, utilised for background reading

-	other	-	-	-	-	-	-	-	Sheppard, Michael; Bronstein, Marcello D.; Freda, Pamela; Serri, Omar; De Marinis, Laura; Naves, Luciana; Rozhinskaya, Liudmila; Hermosillo Reséndiz, Karina; Ruffin, Matthieu; Chen, YinMiao; Colao, Annamaria. Pasireotide LAR maintains inhibition of GH and IGF-1 in patients with acromegaly for up to 25 months: results from the blinded extension phase of a randomized, double-blind, multicenter, Phase III study. Pituitary 2015;18(3):385-394.	-	-	Review article only, referenced in CER summary, utilised for background reading

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	n/a
Updated search terms - Population	acromegaly
Updated search terms - Intervention	pasireotide OR Signifor
Updated search terms - Comparator	octreotide OR pegvisomant OR dopamine agonist OR cabergoline OR bromocriptine OR somatostatin analogue OR ssa
Updated search terms - Outcome	n/a

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	n/a
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist)
	Specific exclusion criteria
	n/a