Evidence Review:
Pasireotide: An injectable medical therapy for the treatment of Cushing's disease

NHS England

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Contents

1. Introduction

Cushing's disease is caused by a tumour of the pituitary gland that secretes high levels of adrenocorticotrophic hormone (ACTH) that in turn drives the adrenal gland to secrete high levels of the hormone cortisol. It is a rare condition with an incidence of 1-2 per million population per year, with a 50% 5-year mortality in the untreated condition.

With modern diagnosis and management, the prognosis is greatly improved although the condition is still associated with considerable morbidity including: cardiovascular disease, infection, hypertension, osteoporosis, depression, and psychosis. Despite treatment, mortality is still significantly higher than control populations, with cardiovascular disease the greatest risk. This is due, in part, to delays in diagnosis and also the availability of effective therapy.

Medical treatment for Cushing's disease is commonly used as second line treatment following pituitary surgery when further curative treatment is planned. The most effective agents currently used are metyrapone and ketoconazole and whilst these medications are effective for the majority of individuals, their usefulness is limited by toxicity in a significant proportion of people. Pasireotide has been proposed as a beneficial, alternative medical therapy used within its licence for those patients who are intolerant to, or whose symptoms are not appropriately managed by, the conventional therapies.

2. Research questions

1. Is pasireotide a clinically effective treatment in adults with Cushing's disease who remain inadequately controlled with conventional therapy?

2. Is pasireotide more or equally effective than comparison therapies in achieving critical and important patient outcomes?

3. Is pasireotide a cost effective treatment in patients with Cushing's disease who remain inadequately controlled with conventional therapy?

4. Is pasireotide more cost effective than comparison therapies?

3. 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.

4. Results

Details of each of the studies reviewed, including a summary of findings, is included in the appendix.

5. Summary of evidence

The evidence for clinical effectiveness of pasireotide in Cushing's disease (CD) comes from a single drug-company sponsored, relatively large, randomised study (Colao et al, 2012). This Phase III trial of pasireotide in CD was a multicentre study that included 162 patients with persistent or recurrent disease or who were ineligible for surgery. 128 patients had a history of pituitary surgery for the treatment of their Cushing's disease, 78 were on medication and 7 had a past history of pituitary irradiation. Patients were randomized to receive pasireotide 600 µg(n = 82) or 900 µg (n = 80) subcutaneously twice daily for 12 months. There were high and similar levels of drop outs in both treatment arms. The rate of drop out remained broadly steady throughout the trial period (29 by month 3, another 26 by month 6 and 29 more by month 12). In total 26 were for adverse events, 37 for lack of efficacy and another 21 either withdrew consent or breached the protocol.

Only the higher initial dose regime arm met the primary outcome measure (normalised urinary free cortisol) – which was a cohort of 53 at month 6. The authors correctly conclude that it would have been unethical to have a non-treatment control group, but also state there was no comparator arm as there is "no approved medical therapy". There are several concerns within the methodology including the lack of a comparator treatment arm and the shifting nature of patients between randomised and open-label participants.

An additional limitation of the Phase III study is the imbalance in baseline UFC levels between the two treatment groups (higher in the 600 µg group), which may have had an effect on outcomes. The mean daily dose of pasireotide in both treatment groups also increased over the 12 months study period (1353 µg/day in 600 µg group vs 1813 µg /day at month 12) suggesting the actual effective dose is likely to be much higher than the 600 µg and 900 µg dosage used in the study. The lack of blinding also increases the possibility of bias in the study - after month 3 only patients who met the primary endpoint continued in a double blind fashion through to month 6 and the rest entered into an open label phase. All patients were entered into an open label phase after 6 months of study. It is likely that this unbinding could have introduced some bias, more so in relation to patient reported outcome measures. As the primary outcome measure was based on urine estimation of UFC, it is recognised that unbinding is unlikely to have influenced the primary outcome measure.

There are two further publications based on data from this trial providing an analysis of the impact of pasireotide on secondary outcome measures (Pivonello et al, 2014) and quality of life (Webb et al, 2014). Decreases in urinary free cortisol from baseline to months 6 and 12 were statistically significant in both treatment groups ($P < 0.001$). Normalisation of urinary free cortisol was more likely to be achieved in patients with lower baseline levels than in patients with higher baseline levels. Most patients (approximately 90%) whose hypercortisolism was uncontrolled (UFC>ULN but with ≤ 50% reduction from baseline) at months 1 and 2 continued to have uncontrolled hypercortisolism at months 6 and 12 indicating patients unlikely to have a response to pasireotide can be identified within the first few months of treatment. Significant improvements in other secondary outcomes measures were seen including systolic blood pressure ($P = 0.03$), diastolic blood pressure ($P = 0.03$), low-density lipoprotein (LDL) cholesterol ($P < 0.001$) and weight ($P < 0.001$).

The impact of pasireotide on quality of life was studied using Cushing QoL. Cushing QoL increased as mUFC levels declined but a statistically significant correlation of -0.40 ($p<0.01$) was observed from baseline to 12 months and not at 6 months. This relation was maintained even after adjusting for number of variables through regression analysis. There was moderately large (0.53) effect sizes for Cushing QoL improvements from baseline to 6 months and 12 months. A strong correlation ($r=-0.70$) was observed between Cushing QoL and Becks Depression Index-II indicating lower QoL was associated with greater depression severity.

Long term effects of pasireotide (up to 4 years) have been reported in two studies (MacKenzie et al, 2014 and Simeoli et al, 2015). Both involved the study of a small number of phase 3 trial patients entering into an extension phase of treatment. Simeoli et al demonstrated that after 24 months of treatment of 8 patients with microadenoma with pasireotide, a significant (>25 %) reduction in tumour volume was found in 62.5 % and in 100 % of patients after 6 and 12 months, respectively. The study by MacKenzie et al, 2014 involved 4 patients in an extension phase, of these two patients had sustained biochemical and clinical response after 9 months of treatment. All 4 patients developed glucose intolerance and complications included second degree atrioventricular block type 1 without QT prolongation in one patient with pre-existing sinus bradycardia, and

symptomatic cholelithiasis requiring cholecystectomy.

There are no published studies evaluating cost effectiveness of pasireotide. Similarly there are no published studies comparing pasireotide with other drugs used in management of Cushing's disease or studies evaluating pasireotide in combination with other drugs used in CD.

The evidence of effectiveness on a number of other drugs used in CD comes from limited number of small retrospective case series with varying definition of primary end point and therefore difficult to compare effectiveness against each other.

Appendix One

Grade	Study design and intervention			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
1+	Systematic	Pasireotide=218, Cabergoline-80, Ketoconazole-143, Metyrapone-76, Mifepristone-46 Mitotane-90	The review included study of following interventions-Pasireotide, Carbengoline, Ketconazole, Metyrapone, Mitatone, Mifepristone	Clinical effectiveness of the intervention	For majority of studies this was 24-h UFC below the ULN. However the definition of ULN varied between studies. For the largest study involving Pasireotide the ULN was 145 nmol/l much below than 276 nmol/l used in another study of Pasireotide (Boscaro et al 2009) Other primary outcome measures were midnight serum cortisol, mean serum or plasma cortisol, Low dose dexamethasone suppression serum cortisol.	Varied from 17% for Pasireotide to 75% for Metyparone. For 3 studies evaluating the Pasireotide the primary endpoint achieved varied form 17% to 29% and the largest of it all by Colao et had a response rate of 26% for 900microgram group	None	None	Gadelha, Mônica R.; Vieira Neto, Leonardo. Efficacy of medical treatment in Cushing's disease: a systematic review. Clin. Endocrinol. (Oxf). 2014	Varied for different medications. For Pasireotide the complications included predominantly hyperglycaemia due to inhibition of insulin secretion (73% of patients study by Colao et al),	Decrease in UFC and blood cortisol, Significant improvement in blood pressure, Low density lipoproteins, and weight from baseline. Other non-significant benefits were facial rubor, supraclavicular and dorsal fat pads, and pituitary tumour volume. However long-term morbidity and mortality data is lacking.	Systematic review by Gadelha et al is a well conducted review of all the drugs used in medical management of Cushings disease. The review had a good study methodology including search strategy, inclusion, exclusion criteria and studies were scored using GRADE system for rating quality of evidence. Six drugs including Pasireotide, Carbegoline, Ketoconazole, Metyrapone, Mitotane and Mifepristone were included in the review, the number of patients for each drug were pooled and the results of primary outcome are given as range. The systematic review highlighted the paucity of quality data for commonly used medications. The majority of the studies are small retrospective case series. The highest level of evidence was found for Pasireotide supported by Colao's randomised controlled trial. However this trial did not compare Pasireotide against placebo or other drugs used in CD therefore achieved grade of 'moderate' level of evidence 'using GRADE. Another prospective multicentre study of Mifepristone which supports its use for treatment of hyperglycaemia in CD but the overall evidence of is low as this study was a small open-label trial (N=50) without comparator group. Higher response rate for achieving primary outcome measures were found for metyrapone, ketoconazole, mitotane, and cabergoline. However the quality of supporting evidence is low because the majority of the studies are small retrospective case series. The definition of primary outcome measures varied between studies and included patients with Cushing's syndrome. PICO questions: 1.Is pasireotide a clinically effective treatment in adults with Cushing's disease who remain inadequately controlled with conventional therapy? Based on one large trial, it showed only 26% who had higher dose of Pasireotide (900 micrograms) achieved primary outcome. For Pasireotide the complications included predominantly hyperglycaemia due to inhibition of insulin secretion (73% of patients study by Colao et al).

2+	Case series	8	pasireotide at the dose of 600-1200 µg	Clinical effectiveness of the intervention	pituitary tumour volume by pituitary MRI, f urinary cortisol levels, at baseline and every 6 months for the entire period of treatment.	A significant (>25 %) reduction in tumour volume was found in 62.5 % and in 100 % of patients, after 6 and 12 months, respectively. In particular, after 6 months, a slight tumour shrinkage (between 25.1 and 50 %) was observed in 25 %, moderate (50.1-75 %) in 25 %, and marked (>75 %) in 12.5 % of patients, whereas after 12 months, a slight tumour shrinkage was observed in 43 %, moderate in 14 %, and marked in 43 % of patients. In 25 % of patients (two patients), a marked tumour shrinkage was recorded, with tumour mass disappearance in one case; this tumour shrinkage was associated to rapid and sustained biochemical remission up to 24 months of continuous pasireotide treatment.	None	-	Simeoli, Chiara; Auriemma, Renata Simona; Tortora, Fabio; De Leo, Monica; Iacuaniello, Davide; Cozzolino, Alessia; De Martino, Maria Cristina; Pivonello, Claudia; Mainolfi, Ciro Gabriele; Rossi, Riccardo; Cirillo, Sossio; Colao, Annamaria; Pivonello, Rosario. The treatment with pasireotide in Cushing's disease: effects of long-term treatment on tumor mass in the experience of a single center. Endocrine. 2015	none recorded	As in primary outcome results	The study was aimed at investigating the effects of long-term treatment with pasireotide (up to 24 months) on tumour mass in a group of patients with Cushing's disease (CD) who had experienced a failure of pituitary surgery or were not candidates for surgery and require medical therapeutic intervention participating in a phase III study. It included eight participants (seven women, one man, aged 38.9 ± 17.6 years). All eight patients (seven with a microadenoma and one with a macroadenoma,) received treatment with pasireotide at the dose of 600-1200 µg bid for at least 6 months. A significant (>25 %) reduction in tumour volume was found in 62.5 % and in 100 % of patients, after 6 and 12 months, respectively. Although the study demonstrated shrinking in tumour size, there is a high risk of chance and confounding impacting the study, due to the small number of patients and lack of details on the baseline of the patients. Therefore the generalisability of the results is poor.

1++	RCT	162 adults with Cushing's disease (82 patients in 600 mcg arm and 80 900mcg arm)	Pasireotide 600 µg and 900 µg	Clinical effectiveness of the intervention	Urinary free cortisol level at or below the upper limit of the normal range at month 6 without an increased dose.	Null hypothesis = no more than 15% of patients would meet the primary end point and an alternative hypothesis that 30% would meet the primary end point and sample size calculated to provide a power of 87%. At six months mean UFC levels were normalised in 15% (95%CI 7 to 22%) and 26% (95%CI 17 to 36%) of patients in the lower and higher dose groups, respectively. The pre-specified criterion for the primary endpoint was only achieved in the higher dose group. The median UFC reduction from baseline to six months was about 48% in both groups. The normalisation rate in the higher dose group was greater for patients with lower baseline UFC levels	Effectiveness of pasireotide on HRQOL, and the relationship between HRQOL and UFC control and other clinical indicators of CD severity using data from the phase III clinical trial (Colao et al) of patients with CD. CushingQoL (a modified HRQoL) was used and improvement in Cushing QoL score >10.1 was used to measure a clinically meaningful change. Beck Depression inventory II was used to measure improvement in depression and mood, higher scores indicating more severe depression. Mean UFC at 3, 6 and 12 months was stratified into UFC controlled, partially controlled and uncontrolled and the relation between mean UFC for different strata was analysed using Spearman's rank for correlation, paried t test for effect size, multivariation regression analysis to adjust number of cofounders and sensitivity analysis at two different doses. The relation between CushingQoL and improvement in clinical symptoms was assessed using Spearman's rank correlation.	Association between Cushing QoL and mUFC- Cushing QoL increased as mUFC levels declined/improved but statistically significant correlation of -0.40 ($p<0.01$) was observed from baseline to 12 months. The affect sizes for CushingQoL improvements from baseline to 6 months and 12 months were moderately large (0.53). Regression analysis adjusting for covariates, expected CushingQoL score at month 12 was 58.3 for mUFC controlled (Δ11.5 vs uncontrolled, P=0.012), 54.5 for partially controlled (Δ7.7 vs uncontrolled, P=0.170), and 46.8 for uncontrolled. Association between CushingQoL and CD symptoms and signs- A strong correlation (r=-0.70) was observed between CushingQoL and BDI-II indicating lower QoL was associated with greater depression severity. However no correlation was observed between changes in CushingQoL and changes n waist circumference, blood pressure, facial rubor, striae, bruising, supraclavicular fat pad and dorsal fat pad.	Webb, Susan M.; Ware, John E.; Forsythe, Anna; Yang, Min; Badia, Xavier; Nelson, Lauren M.; Signorovitch, James E.; McLeod, Lori; Maldonado, Mario; Zgliczynski, Wojciech; de Block, Christophe; Portocarrero-Ortiz, Lesly; Gadelha, Monica. Treatment effectiveness of pasireotide on health-related quality of life in patients with Cushing's disease. Eur. J. Endocrinol. . 2014	Not included	As in secondary outcome results however long term impact of Pasireotide on Cushing HRQOL in relation to mUFC are unknown	This paper is a detailed analysis of secondary endpoints for patients with confirmed persistent, recurrent or de novo Cushing's Disease. The majority of these patients were post pituitary surgery and a number of them were receiving a combination of Cushing's Disease medications, for which details were not available. The objectives of this study were to investigate the treatment effectiveness of pasireotide on HRQOL, and to assess the relationship between HRQOL and UFC control and other indicators of CD severity using data from the phase III clinical trial of patients with CD. The authors report that there is a significant association between Cushing QoL and mUFC. Cushing QoL increased as mUFC levels declined/improved but statistically significant correlation of -0.40 ($p<0.01$) was observed from baseline to 12 months and not at 6 months. The affect sizes for CushingQoL improvements from baseline to 6 months and 12 months were moderately large (0.53). Regression analysis adjusting for covariates, expected CushingQoL score at month 12 was 58.3 for mUFC controlled (Δ11.5 vs uncontrolled, P=0.012), 54.5 for partially controlled (Δ7.7 vs uncontrolled, P=0.170), and 46.8 for uncontrolled. A strong correlation (r=-0.70) was observed between CushingQoL and BDI-II indicating lower QoL was associated with greater depression severity. However no correlation was observed between changes in CushingQoL and changes n waist circumference, blood pressure, facial rubor, striae, bruising, supraclavicular fat pad and dorsal fat pad. Overall this is a quality study analysed using valid statistical methods including regression analysis, sensitive analysis, effect size for association between Cushing QoL and mUFC and CushingQoL and clinical signs and symptoms of CD. The study has some limitations including lack of comparator, open label dose after 6 months and potential bias in patient reported HRQoL, and lack of impact of different doses on HRQoL as number of patients received dose escalation during the study. PICO questions:.1. Is pasireotide a clinically effective treatment in adults with Cushing's disease who remain inadequately controlled with conventional therapy? Yes it appears significant association between Cushing QoL and mUFC, Cushing QoL increased as mUFC levels declined/improved. 2. Is pasireotide more effective than the comparison therapies (listed above) in achieving the critical and important patient outcomes as detailed above? Cannot be answered as there was no comparator used in the study. 3. Is pasireotide a cost effective treatment in patients with Cushing's disease who remain inadequately controlled with conventional therapy? Can't be answered as the trial did not include cost effective analysis. 4. Is pasireotide more cost effective than comparison therapies (listed above) ? Cant be answered as the trial did not include cost effective analysis.

1++	RCT	162 adults with Cushing's disease (82 patients in 600 mcg arm and 80 900mcg arm)	Pasireotide 600 µg and 900 µg	Clinical effectiveness of the intervention	Urinary free cortisol level at or below the upper limit of the normal range at month 6 without an increased dose.	Null hypothesis = no more than 15% of patients would meet the primary end point and an alternative hypothesis that 30% would meet the primary end point and sample size calculated to provide a power of 87%. At six months mean UFC levels were normalised in 15% (95%CI 7 to 22%) and 26% (95%CI 17 to 36%) of patients in the lower and higher dose groups, respectively. The pre-specified criterion for the primary endpoint was only achieved in the higher dose group. The normalisation rate in the higher dose group was greater for patients with lower baseline UFC levels	Changes in signs and symptoms of hypercortisolism including blood pressure, cholesterol, LDL-cholesterol, weight, HRQoLat months 6 and 12 were assessed in relation to the degree of UFC response at baseline and at month 6.	In an initial paper on this trial by Coale et al (2012) reported a significant reduction in systolic blood pressure (-6.1 mmHg), diastolic blood pressure (-3.7 mm Hg), triglycerides(-0.2 mmol/lit), LDL cholesterol (-0.4 mmol/lit), and weight (-6.7 kgs) at 12 months when compared to baseline. HRQoL increased by 11.1 points at 12 months from baseline. In this paper authors present the same analysis but by 3 different strats of UFC -controlled (UFC≤ULN) , partial control (UFC>ULN but with ≥50% reduction from baseline) and uncontrolled (UFC>ULN but with ≤ 50% reduction from baseline). For blood pressure there was decrease in SBP and DBP in all the 3 UFC strata but were larger in controlled category than in partially controlled or not controlled UFC categories. BMI, weight and waist circumference decreased throughout the study. BMI was significantly reduced at months 6 and 12 and were achieved in patients from all response groups at months 6 and 12. Significant reductions in weight were also seen at months and 12. Reductions were observed at both time points without full UFC control but were greatest in patients with controlled UFC. Decreases in waist circumference were achieved in patients from all response groups with no clear difference between the response subgroups at months 6 and 12. Cholesterol, LDL cholesterol reduced in all the three response group at month 6 and 12. However significant reduction was seen in controlled and uncontrolled UFC but not in partial control group. Authors do not give a reason for this finding. ?small numbers. Changes in BDI-II and HRQoL- BDI-II score significant improvements were seen from baseline to months 6 and month 12 in all UFC response subgroups. Similarly improvement in HRQoL were seen at month 6 and month 12 in the three UFC groups and was statistically significant in all except in uncontrolled group at month 12. For changes in rubor, striae, and fat pad, at months 6 and 12 majority of patients had no improvement or just improved by one category (severe to moderate or moderate to none). No changes to bone mineral density were observed and there was minimal change in muscle strength in three UFC control groups. Significant reduction in total body fat mass and lean body mass were observed in patients in the three UFC control groups. In an initial paper on this trial by Coale et al (2012) reported a significant reduction in systolic blood pressure (-6.1 mmHg), diastolic blood pressure (-3.7 mm Hg), triglycerides(-0.2 mmol/lit), LDL cholesterol (-0.4 mmol/lit), and weight (-6.7 kgs) at 12 months when compared to baseline. HRQoL increased by 11.1 points at 12 months from baseline. In this paper authors present the same analysis but by 3 different strats of UFC -controlled (UFC≤ULN) , partial control (UFC>ULN but with ≥50% reduction from baseline) and uncontrolled (UFC>ULN but with ≤ 50% reduction from baseline). For blood pressure there was decrease in SBP and DBP in all the 3 UFC strata but were larger in controlled category than in partially controlled or not controlled UFC categories. BMI, weight and waist circumference decreased throughout the study. BMI was significantly reduced at months 6 and 12 and were achieved in patients from all response groups at months 6 and 12. Significant reductions in weight were also seen at months and 12. Reductions were observed at both time points without full UFC control but were greatest in patients with controlled UFC. Decreases in waist circumference were achieved in patients from all response groups with no clear difference between the response subgroups at months 6 and 12. Cholesterol, LDL cholesterol reduced in all the three response group at month 6 and 12. However significant reduction was seen in controlled and uncontrolled UFC but not in partial control group. Authors do not give a reason for this finding. ?small numbers. Changes in BDI-II and HRQoL- BDI-II score significant improvements were seen from baseline to months 6 and month 12 in all UFC response subgroups. Similarly improvement in HRQoL were seen at month 6 and month 12 in the three UFC groups and was statistically significant in all except in uncontrolled group at month 12. For changes in rubor, striae, and fat pad, at months 6 and 12 majority of patients had no improvement or just improved by one category (severe to moderate or moderate to none). No changes to bone mineral density were observed and there was minimal change in muscle strength in three UFC control groups. Significant reduction in total body fat mass and lean body mass were observed in patients in the three UFC control groups.	Pivonello, Rosario; Petersenn, Stephan; Newell-Price, John; Findling, James W.; Gu, Feng; Maldonado, Mario; Trovato, Andrew; Hughes, Gareth; Salgado, Luiz R.; Lacroix, André; Schopohl, Jochen; Biller, Beverly M. K.; Pasireotide B2305 Study Group. Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study. Clin. Endocrinol. (Oxf). 2014	Hyperglycemia-related adverse events occurred in 73% of patients, and 6% of patients discontinued the study treatment because of such events. Grade 1 and 2 adverse drug reactions in 57% of patients; grade 3 in 36%, and grade 4 in 3%. Grade three and four mostly due to hyperglycaemic events. No deaths reported during treatment.	As in secondary outcome measures. Authors also state that there were improvements in signs and symptoms of patients who did not achieve normal urinary free cortisol levels	This paper is a detailed analysis of secondary endpoints i.e. clinical response and symptomatic relief associated with reduction in UFC at 6 months and 12 months follow-up of patients in trial by Colao et al. Authors report pasireotide treatment was associated with significant improvements in SBP, DBP, total cholesterol, LDL-cholesterol, weight, BMI, waist circumference and HRQoL at 6 and 12 months. Authors report reduction on BP, BMI and weight were seen in all three groups of controlled, partial control and uncontrolled and the maximum improvements were seen controlled group compared to partial and uncontrolled groups. Similarly Becks Depression II score and HRQoL improved in all three UFC at months 6 and 12 in all UFC groups. For cholesterol and LDL cholesterol significant reduction was seen controlled and uncontrolled groups but not in partial controlled group. Authors do not give a reason for this phenomena. The study has some limitation including possible confounding from failure to adjust for impact of these concomitant medications used by patients to manage comorbidities, role of chance due to large dropout rate at 12 months, and small number of patients in subgroup analysis. PICO questions:.1. Is pasireotide a clinically effective treatment in adults with Cushing's disease who remain inadequately controlled with conventional therapy? There is good evidence that 29% who had higher dose of Pasireotide (900 micrograms) achieved primary outcome measure. For secondary endpoints patients who achieved good control (UFC less than upper limit normal) had significant improvements in SBP, DBP, total cholesterol, LDL-cholesterol, weight, BMI, waist circumference and HRQoL at 6 and 12 months . However chance and role of confounders cannot be ruled out. 2. Is pasireotide more effective than the comparison therapies (listed above) in achieving the critical and important patient outcomes as detailed above? Cannot be answered as there was no comparator used in the study. 3. Is pasireotide a cost effective treatment in patients with Cushing's disease who remain inadequately controlled with conventional therapy? Can't answer as the trial did not include cost effective analysis. 4. Is pasireotide more cost effective than comparison therapies (listed above) ? Cant answer as the trial did not include cost effective analysis.

3	Case series	4	Pasireotide	Clinical effectiveness of the intervention	urinary free cortisol	2 patients had clinical and biochemical remission	clinical worsening of glycaemic control	All 4 patients developed glucose intolerance; however, the two patients in the extension phase were eventually able to discontinue all diabetes pharmacotherapy	MacKenzie Feder, Jessica; Bourdeau, Isabelle; Vallette, Sophie; Beauregard, Hugues; Ste-Marie, Louis-Georges; Lacroix, André. Pasireotide monotherapy in Cushing's disease: a single-centre experience with 5-year extension of phase III Trial. Pituitary. 2014	-	-	This is a follow-up study of 4 patients from a phase 3 trial. Data is not clearly presented for success for primary and secondary outcomes. But it appears from the abstract that 50% had clinical and biochemical benefits. All 4 had abnormal glucose tolerance but subsequently improved. It is not possible to draw any conclusion from the study due to the small sample size.

3	RCT	18	pasireotide 600 µg sc bid	Clinical effectiveness of the intervention	urinary free cortisol	Of the 38 patients who completed the core study, 19 entered the extension and 18 were included in the efficacy analyses (three responders, 11 reducers, four non-reducers in the core study). At data cut-off, median treatment duration in the extension was 9.7 months (range: 2 months to 4.8 years). At extension month 6, 56% of the 18 patients had lower UFC than at core baseline and 22% had normalized UFC	serum cortisol, plasma adrenocorticotropic hormone, body weight and diastolic blood pressure	Lowering of serum cortisol, plasma adrenocorticotropic hormone, body weight and diastolic blood pressure	Boscaro, M.; Bertherat, J.; Findling, J.; Fleseriu, M.; Atkinson, A. B.; Petersenn, S.; Schopohl, J.; Snyder, P.; Hughes, G.; Trovato, A.; Hu, K.; Maldonado, M.; Biller, B. M. K.. Extended treatment of Cushing's disease with pasireotide: results from a 2-year, Phase II study. Pituitary. 2014	The most common adverse events were mild-to-moderate gastrointestinal disorders and hyperglycaemia.	As in primary and secondary outcome	This was a planned, open-ended, single-arm, multicentre extension study (primary endpoint: 6 months). Patients aged ≥18 years with Cushing's disease who completed the core study could enter the extension if they achieved UFC normalization at core study end and/or obtained significant clinical benefit. 19 entered the extension and 18 were included in the efficacy analyses (three responders, 11 reducers, four non-reducers in the core study). At data cut-off, median treatment duration in the extension was 9.7 months (range: 2 months to 4.8 years). At extension month 6, 56% of the 18 patients had lower UFC than at core baseline and 22% had normalized UFC. Of the four patients who remained on study drug at month 24, one had normalized UFC. As a phase 2 trial this study establishes effectiveness of Paseriotide for the extended treatment of some patients with Cushing's disease. However the study limited due to small sample size, and lack of comparator data
1++	RCT	162 adults with Cushing's disease	Pasireotide 600 µg and 900 µg	Clinical effectiveness of the intervent	Urinary free cortisol level at or below the upper limit of the normal range at month 6 without an increased dose.	Null hypothesis = no more than 15% of patients would meet the primary end point and an alternative hypothesis that 30% would meet the primary end point and sample size calculated to provide a power of 87%. At six months mean UFC levels were normalised without a prior dose increase in 15% (95%CI 7 to 22%) and 26% (95%CI 17 to 36%) of patients in the lower and higher dose groups, respectively.	Changes in signs and symptoms of hypercortisolism including blood pressure, cholesterol, LDL-cholesterol, weight, HRQoLat months 6 and 12 were assessed in relation to the degree of UFC response at baseline and at month 6.	Non significant reduction in mean plasma coricotropin, salivary cortisol and a significant reduction in systolic blood pressure (-6.1 mmHg), diastolic blood pressure (-3.7 mm Hg), triglycerides(-0.2 mmol/lit), LDL cholesterol (-0.4 mmol/lit), and weight (-6.7 kgs) at 12 months when compared to baseline. HRQoL increased by 11.1 points at 12 months from baseline. (data on above analysed at 3 different levels of mUFC is included in study by Pivonello et al 2014.	Colao, Annamaria; Petersenn, Stephan; Newell-Price, John; Findling, James W.; Gu, Feng; Maldonado, Mario; Schoenherr	Hyperglycemia-related adverse events occurred in 73% of patients, and 6% of patients discontin	As in secondary outcome measures. Authors also state that there were improve	This is a single, relatively large, high quality randomised study of Pasireotide. The study had 135 patients with persistent or recurring Cushing's disease and 27 newly diagnosed patients who were not candidates for surgery. 128 patients had a history of pituitary surgery for the treatment of their Cushing's Disease, 78 were on medication and 7 had a past history of pituitary irradiation. The results of primary or secondary outcomes are not available by these sub-groups. The wider application of this study to clinical practice is limited by being a comparison of two doses of pasireotide, limited period of blinding (3/12) and not including a control group. Only one-third of patients in higher dose group met primary outcome measures after three months. However the proportion of patients whose baseline UFC was 5 times the ULN

		(82 patients in 600 µg arm and 8090 0µg arm)		ion		Thus the pre-specified criterion for the primary endpoint was only achieved in the higher dose group. The normalisation rate in the higher dose group was greater for patients with lower baseline UFC levels. With the inclusion of patients who had an increased dose at month 3, 16% (95% CI, 8 to 24) of patients in the 600-µg group and 29% (95% CI, 19 to 39) of those in the 900-µg group had normalized urinary free cortisol levels at month 6. At month 12, urinary free cortisol levels at or below the upper limit of the normal range was maintained in 13% (95% CI, 6 to 21) of patients in the 600-µg group and 25% (95% CI, 16 to 35) of those in the 900-µg group thus showing a large number of patients who responded , reductions were sustained at month 12. However this data is not adjusted for increased doses that patients may have received as part of escalation. Overall patients with lower baseline urinary free cortisol level (≤ 5 times the upper limit of the normal range) had a higher rate of response which was sustained at month 12. This was higher in higher dose group compared to lower dose group.			, Ulrike; Mills, David; Salgado, Luiz Roberto; Biller, Beverly M. K.; Pasireotide B2305 Study Group. A 12-month phase 3 study of pasireotide in Cushing's disease. N. Engl. J. Med.. 2012	ued the study treatment because of such events. Grade 1 and 2 adverse drug reactions in 57% of patients; grade 3 in 36%, and grade 4 in 3%. Grade three and four mostly due to hypergly caemic events. No deaths reported during treatment.	ments in signs and symptoms of patients who did not achieve normal urinary free cortisol levels	was higher in 600µg group (48%, median UFC, 730nmol/24) than 900µg group (28%, median UFC 487 nmol/L) dose group which could have biased the results. Patients with lower baseline UFC had higher normalisation rate and were sustained at month 12. Patients also demonstrated significant improvement in health manifestations of CD including reduction in BP, cholesterol, weight and triglycerides and improvement HRQoL. These improvements were just not limited to those who achieved a normal UFC but to even in partially controlled and uncontrolled UFC groups. However for the above variable the data from two study arms are combined and therefore it is difficult comment on impact of dosage on the results. The treatment has also significant adverse events including hyperglycaemia (73%) and discontinuation rate of 6%. Grade 1 and 2 adverse drug reactions occurred in 57% of patients; grade 3 in 36% and grade 4 in 3% (the grade 3 and 4 were mostly due to hyperglycaemic events). No deaths were reported during treatment. Further long-term evaluation of these side effects are needed. It is also worth noting that the mean daily dose of pasireotide in both treatment groups increased over 12 months study period (1353µg/day in 600µg group vs 1813 µg/day at month 12) suggesting the actual effective dose is likely to much higher than 600µg and 900 µg dosage used in the study. PICO questions:.1. Is pasireotide a clinically effective treatment in adults with Cushing's disease who remain inadequately controlled with conventional therapy? There is good evidence that 29% who had higher dose of Pasireotide (900 micrograms) achieved primary outcome measure. For secondary endpoints patients who achieved good control (UFC less than upper limit normal) had significant improvements in SBP, DBP, total cholesterol, LDL-cholesterol, weight, BMI, waist circumference and HRQoL at 6 and 12 months . However chance and role of confounders cannot be ruled out. 2. Is pasireotide more effective than the comparison therapies (listed above) in achieving the critical and important patient outcomes as detailed above? Cannot be answered as there was no comparator used in the study. 3. Is pasireotide a cost effective treatment in patients with Cushing's disease who remain inadequately controlled with conventional therapy? Can't answer as the trial did not include cost effective analysis. 4. Is pasireotide more cost effective than comparison therapies (listed above)? Can't answer as the trial did not include cost effective analysis.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	Not provided
Updated search terms - Population	Cushing's disease Pituitary adenoma Hypercortisolism Cushing disease Inappropriate ACTH Secretion Syndrome Inappropriate Adrenocorticotropic Hormone Secretion Pituitary-Dependant Hypercortisolism Pituitary ACTH Hypersecretion Cancer of the pituitary Pituitary Cancer Pituitary Tumours Pituitary Carcinoma
Updated search terms - Intervention	Pasireotide Signifor Somatostatin analogue Somatostatin analog SST analogue SST analog SOM 230 SOM230 SOM-230
Updated search terms - Comparator	Ketoconazole Zorinax Nizoral R-41400 R41,400 14-alpha Demethylase Inhibitors Cytochrome P-450 CYP3A Inhibitors Metyrapone

	Methopyrapone Metopiron Metopirone SU 4885
Updated search terms - Outcome	Not applicable
Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, the following are included: 1. All relevant systemic 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 reach 30, inclusion stops here 3. All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 4. All relevant non analytical studies (case series/ reports etc) that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 5. Expert opinion
	Specific inclusion criteria
	English language <5 years, <10 years RCTs, SRs, MAs Title/Abstract
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Do not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (except where there are fewer than 10 studies overall) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site
	Specific exclusion criteria