PEGVISOMANT FOR ACROMEGALY

QUESTION(S) TO BE ADDRESSED:

1. a) What is the clinical effectiveness of pegvisomant in achieving the patient outcomes of interest in patients with acromegaly?
   b) Is there evidence that pegvisomant is more effective in some patient subgroups than others?
   c) In people treated for acromegaly how strongly are Insulin Growth Factor–1 (IGF-1) and Growth Hormone (GH) measurements associated with long term mortality?

2. What is the safety and tolerability of pegvisomant in terms of:

   - Liver dysfunction
   - Pituitary tumour growth
   - Other side effects?

3. How cost effective is pegvisomant in:

   a) Patients with acromegaly who remain inadequately controlled with conventional therapy (monotherapy) compared to alternatives or no treatment?
   b) Patients with acromegaly who remain on dopamine agonists or somatostatin analogues (SSAs) (combination therapy) compared to alternatives or no treatment?

4. Supplementary questions

   a) At what stage in the course of the disease would patients most benefit from using pegvisomant, as either monotherapy or combination therapy, to treat their acromegaly?
   b) Which patient groups would most benefit from the use of combination therapy (i.e. pegvisomant with SSA)?
   c) If there is optimal dose of pegvisomant as a monotherapy?
   d) If there is an optimal dose of pegvisomant as a combination therapy?

SUMMARY

Background

- Acromegaly is a rare endocrine disorder resulting from excessive secretion of growth hormone (GH). The underlying cause in more than 99 percent of patients is a benign adenoma of the GH-secreting cells of the anterior pituitary. Very rarely, acromegaly is due to a malignant pituitary neoplasm, hypothalamic over-secretion of growth hormone releasing hormone (GHRH) or to extra-pituitary tumours that secrete GH or GHRH.
- The first-line treatment option is surgery which fails in around 40 percent of patients.
- Radiotherapy has a role in the management of patients with active acromegaly after surgery to prevent progression of residual tumour.
- Between 20 and 50 percent of patients will still have persistently active disease following surgery and radiotherapy.
- Currently available medical therapies include dopaminergic agonists, somatostatin analogues and a growth hormone receptor antagonist – pegvisomant.
- Pegvisomant (PEG) was granted a European licence for the use in the treatment of acromegaly in 2002.

- Administration is by subcutaneous injection, with a loading dose of 80 mg, then 10 mg daily, increased in steps of 5 mg daily according to response with a maximum dose of 30 mg a day.

Clinical Effectiveness

We found one systematic review[1] and seven[2-8] reports of four randomised controlled trials (RCTs) that assessed the clinical effectiveness of pegvisomant as therapy for acromegaly. . The systematic review was used for cost effectiveness information only since it combined observational data with limited information on outcomes from one RCT. The three publications of this RCT have been covered in more depth in this report.[2, 7, 8] The RCTs ranged in sample size from 18 to 118 and were of good to moderate quality, with two providing power calculations,[3, 6] two being double-blinded[6, 8] and one stating that treatment group allocation was concealed;[8] none of the RCTs indicated how the randomisation sequence was generated. The RCTs lasted between three months and one year, and included a range of participants – including those who were medication therapy and radiation naïve, those who had responded to SSAs, and those who had received other treatments but were not currently taking SSAs. Not all of these populations correspond to the licensed indication for pegvisomant.

Two meta-analyses[9,10] and two observational studies [11, 12] were identified that assessed the link between IGF-1 and mortality. One meta-analysis contained 4,806 participants from 18 observational studies; the number of participants in the second meta-analysis was not specified. The two observational studies included 442 and 1,512 participants.

- Only one RCT of pegvisomant (n=118) reported on mortality, and found no difference between pegvisomant monotherapy and octreotide over one year in those who were medication therapy and radiation naïve (one death (2%) in each group).[3]
- Four studies investigated the association between IGF-1 levels and mortality in people with acromegaly receiving any treatment.[9-12] Of these, the systematic review found an overall increased risk of mortality for people with acromegaly compared to the general population.[9] In contrast, those who achieved normal IGF-1 or GH levels were no longer at elevated mortality risk.
- The effect of pegvisomant on IGF-1 levels and normalisation (achieving IGF-1 levels within the normal range) was investigated in four RCTs.[3, 5, 6, 8]
- Pegvisomant monotherapy achieved IGF-1 normalisation in a greater proportion of participants than placebo (n=112; 10% of participants on placebo vs 54% on pegvisomant 10mg, p=0.02; vs 81% on pegvisomant 15mg, p<0.001; vs 89% on pegvisomant 20mg, p<0.001) and octreotide (n=118; 34% octreotide vs 51% pegvisomant, p=0.09).[3, 8] A dosage of 20mg pegvisomant per day appeared to give the best rates of IGF-1 normalisation in the placebo controlled trial.[8]
- Pegvisomant monotherapy did not differ significantly from octreotide (an SSA) in the proportion of participants achieving normal IGF-1 levels.[3] However, the reduction in IGF-1 levels from baseline was greater with pegvisomant than with octreotide after 24 weeks (– 53% (standard deviation [SD] 26.3) vs – 42% (SD 28.7), p=0.04) and 52 weeks (– 55% (SD 32.9) vs – 43% (SD 30.3), p=0.04).[3] The estimated difference between the groups was 12 percent (p=0.05). For participants with higher IGF-1 levels at baseline, pegvisomant achieved greater reductions in mean IGF-1 levels than octreotide (mean reduction –59% vs –44%, p=0.03).
- Combination treatment with pegvisomant (15–30 mg twice per week) and lower dose SSA (half the usual dosage: octreotide long release 6.7 to 20 mg per four weeks or lanreotide Autogel from 24 to 60 mg per four weeks) in SSA responders did not differ significantly from SSA monotherapy (octreotide long-acting release 10 to 30 mg per four weeks or

lanreotide Autogel 40 to20 mg per four weeks) with respect to IGF-1 levels after 24 weeks.[5]

- GH levels were described in four RCTs.[3, 5, 6, 8] When compared with placebo, pegvisomant (PEG) significantly increased GH levels from baseline to three months (mean change PEG 11.2 µg/L (standard error [SE] 2.4) vs placebo 0.0 µg/L (SE 2.2), p=0.0013).[7] Another study which examined different doses found that, when compared to placebo, the change from baseline to three months in GH level was significant for those receiving 15mg or 20mg pegvisomant per day, but not those receiving 10mg.[8]
- Musculoskeletal outcomes were assessed in one study.[2] A significant decrease in bone turnover markers was observed in the pegvisomant group from baseline.
- Quality of life (QoL) with pegvisomant treatment was compared in two trials.[3, 6] Significant improvement from baseline in overall disease-specific quality of life (measured using the AcroQoL and PASQ tools) was seen with pegvisomant when compared to placebo, in patients already taking an SSA.[6] When looking at AcroQoL overall quality of life, a significantly greater improvement from baseline was found with pegvisomant compared to placebo (110 point scale, higher scores indicate better QoL; change from baseline: PEG 6.4 +/- 4.25% placebo -1.1 +/- 7.12% p=0.008). AcroQol physical quality of life also improved with pegvisomant compared with placebo (p=0.002), but no significant difference was seen for psychological quality of life (p=0.185). Some domains on the PASQ tool did not significantly change from baseline with pegvisomant (joint pain, headache, fatigue, and numbness of tingling of extremities), but an improvement was seen for QoL related to soft tissue swelling, excessive sweating and overall health status compared to placebo.[6] PASQ scores for change from baseline (median+/- SD) between pegvisomant and placebo were: total score (48 point scale, higher score indicates worse QoL; PEG -2.0 +/- 6.60, placebo 1.5 +/- 5.02, (p=0.038), soft tissue swelling (8 point scale for individual symptom scores; PEG -0.5 +/- 1.37, placebo 0.0 +/- 1.28, p=0.024), excessive sweating (PEG 0.0 +/- 1.79, placebo 0.5 +/- 0.98, p= 0.036), overall health status (PEG -1.0 +/- 1.99, placebo 0.5 +/- 1.36, p=0.035), and joint pain (PEG -1.0 +/-1.47, placebo 0.0 +/- 1.49, p=0.083). Overall improvement in AcroQoL scores from baseline was greater with pegvisomant than octreotide in a second trial, but this difference was not significant (mean change 7.2 (SD 16.4) vs 6.9 (SD 13.3) respectively; p value > 0.05 but not specified).[3]
- One placebo-controlled study assessed clinical signs and symptoms via questionnaire and found that, after 12 weeks, total and fatigue scores improved in all three pegvisomant dosage groups (10mg, 15mg, 20mg); scores for ring size, soft tissue swelling and excessive perspiration improved significantly compared with placebo for those on 15mg and 20mg pegvisomant but not 10mg.[8]

Cost Effectiveness

- One study was identified which evaluated cost effectiveness relative to standard care in the UK as part of a systematic review.[1] Using the cost and effectiveness assumptions in this study, the model showed that over a 20 year period the cost effectiveness of PEG was very unlikely to fall below £80,000 per quality adjusted life year gained (QALY) or £212,000 per life year gained.
- On this basis, pegvisomant is unlikely to represent good value for money when considered against the current standards typically applied to interventions in the UK National Health Service.

Safety

- Pegvisomant has a number of associated safety concerns and adverse events, the more serious of which are changes to blood sugar levels and liver problems.[13]
- Changes to blood sugar levels were assessed in three RCTs.[3, 5, 8] When compared with placebo pegvisomant monotherapy did not show any significant difference in blood sugar,

fasting glucose or insulin levels.[8] A similar outcome was seen for pegvisomant combination therapy compared to SSA where no difference was seen for glucose levels.[5] However, when compared with octreotide, mean fasting glucose levels decreased significantly more with pegvisomant in both diabetic and non-diabetic participants (overall p=0.0001).[3] It is noted that people with diabetes treated with pegvisomant should be carefully monitored and doses of anti-diabetic drugs reduced as necessary.[13]

- Changes in levels of the liver enzymes alanine transaminase (ALT) from baseline to week 24 were not significantly different when pegvisomant combined with SSA was compared to SSA alone (median (range) 5.5 Units/Litre (U/L) (-5 to 173) vs 0.5 U/L (-7 to 5) respectively, p= 0.06).[4]
- Pituitary tumour size was reported in two RCTs comparing pegvisomant to placebo [8] or octreotide. [3] No difference in change in tumour volume from baseline was found between groups in either study.
- One RCT found a similar proportion of people experienced adverse events with pegvisomant and octreotide.[3]

1 Context

1.1 Introduction

Acromegaly is a rare endocrine disorder resulting from excessive secretion of growth hormone (GH). The underlying cause in more than 99 percent of patients is a benign adenoma of the GH-secreting cells of the anterior pituitary. Very rarely, acromegaly is due to a malignant pituitary neoplasm, hypothalamic over- secretion of growth hormone releasing hormone (GHRH) or to extra-pituitary tumours that secrete GH or GHRH.

The main feature of acromegaly is over-growth of body tissue. This is due to the excessive levels of GH prompting increased production of the hormone insulin-like growth factor 1 (IGF-1) by the liver, which in turn increases growth of muscle, cartilage and bone. Signs and symptoms of the condition include large facial features and unusually large hands and feet, as well as fatigue, joint pain, and obstructive sleep apnoea.
If the condition is untreated, it increases the risk of other conditions such as type 2 diabetes, high blood pressure, cardiovascular disease and arthritis.

The first-line treatment option is surgery. However, the success of surgery depends on the size and invasive characteristics of the tumour. Transsphenoidal surgery cures around 60 percent of patients.

Radiotherapy has a role in the management of patients with active acromegaly after surgery to prevent progression of residual tumour but it has a slow onset of effect and may take years or decades for GH levels to fall. There is also a risk that radiotherapy may lead to hypopituitarism. Between 20 and 50 percent of patients will still have persistently active disease following surgery and radiotherapy.

Currently available medical therapies are dopaminergic agonists and somatostatin analogues (SSAs), such as octreotide, and lanreotide, –which inhibit GH secretion or production - and pegvisomant - a growth hormone (GH) receptor antagonist.[14] Pegvisomant was granted a European licence for the use in the treatment of acromegaly in 2002.[15] It is indicated for adults with acromegaly who have not responded to surgical and/or radiation therapy and SSAs or who are unable to tolerate SSAs.

1.2 Existing national policies and guidance

There are no current policies or guidance from the National Institute for Health and Care Excellence (NICE) regarding the use of pegvisomant for acromegaly.

2 Epidemiology

It is estimated that around 4 to 13 in every 100,000 people may have acromegaly, equivalent to between 2,500 and 8,300 people living with the condition in the UK.[14]

Acromegaly can affect people of any age, but it is rare in children. The average age at which people are diagnosed is around 40 to 45 years old.

The life expectancy of a person with acromegaly if left untreated is reduced by approximately 10 years.[16] Acromegaly is known to have increased mortality rates due to cardiovascular and cerebrovascular events, respiratory complications and malignant neoplasms.[12]

3 The intervention

Pegvisomant is a protein of recombinant DNA origin. It is an analogue of human GH which has been structurally altered to act as a GH receptor antagonist. Pegvisomant binds highly selectively to the GH receptor and it does not bind to other receptors such as the prolactin receptor (to which GH binds).[8, 13]

By binding to GH receptors, pegvisomant inhibits the action of GH leading to decreased production of insulin-like growth factor-1 (IGF-1) and other growth hormone responsive serum proteins.[13]

Pegvisomant is used to treat acromegaly in patients where the condition cannot be controlled by surgery or radiation, or SSAs. It is administered subcutaneously, initially as a one-off loading dose of 80mg, followed by daily doses of 10mg. Response should be reviewed every four to six weeks, and the dose can be titrated up as needed to a maximum of 30 mg per day. The patient or their caregiver can be trained to administer the injections.[15]

Pegvisomant is sometimes used in combination with an SSA or dopamine agonist, where there has been a partial response, although combination therapy is not explicitly described in the licenced usage and indications.

4 Findings

4.1 Evidence of effectiveness

Medline, Embase and Cochrane were searched from 1995 onwards for systematic reviews, randomised controlled trials (RCTs), controlled studies and cohort studies comparing the use of pegvisomant monotherapy or combination therapy with somatostatin analogues, dopamine agonists, transsphenoidal surgery, radiotherapy or placebo (see section 8 for further details of search strategy). Randomised studies were included if they contained 15 participants or more and cohort studies if they included more than 400 participants. Case series were excluded, as were conference reports and studies where the population had been reported in other, more recent,

studies. An additional search was performed in PubMed to identify studies investigating the impact of IGF-1 and GH on mortality outcomes in acromegaly.

One systematic review[1], two meta-analyses[9, 10], seven reports of four RCTs[2-8] and two observational studies met the inclusion criteria. The studies were mainly carried out in the US and Europe.

The systematic review[1] and seven[2-8] reports of four subsequent randomised controlled trials (RCTs) assessed the clinical effectiveness of pegvisomant as therapy for acromegaly. Three publications provided data on different outcomes relating to a single RCT. [2, 7, 8]

The systematic review was well conducted with a clear question, set inclusion and exclusion criteria and quality assessment for included studies. However, this SR was used for cost effectiveness information only since it combined a heterogeneity of study types, three reports of one RCT, 14 uncontrolled before and after studies and one case series and provided limited information on outcomes from the included RCT.[1] The three publications of this RCT have been covered in more depth in this report.[2, 7, 8]

The RCTs ranged in sample size from 18 to 118 and were of moderate quality. A double-blind RCT compared pegvisomant to placebo and had a low risk of bias.[8] In this study participants were well balanced between groups except with respect to previous therapy received and serum GH and IGF-1 levels. No indication was given whether these differences were of statistical significance. One RCT comparing pegvisomant monotherapy to octreotide had moderate risk of bias.[3] This study had no indication of concealed allocation to study group. The study had performed a power calculation to ensure enough participants were recruited to statistically detect the anticipated difference between groups. No information was provided on the distribution of participants who had received prior surgical therapy between groups. There were no statistically significant differences between groups at baseline and all participants were accounted for in the analysis.

Two trials compared pegvisomant plus SSA (combination therapy) to placebo plus SSA[6] and SSA alone.[5] Both were of moderate risk of bias. The placebo controlled trial was a double-blind crossover trial and all participants were analysed. Baseline characteristics were not given for each group, only the entire trial population. This study also conducted calculations to ensure the study was adequately powered. The trial comparing pegvisomant combination therapy to SSA alone was randomised but non-blinded. There were no statistically significant differences between groups at baseline.

None of the included RCTs indicated how the randomisation sequence was generated. The RCTs lasted between three months and one year, and included a range of participants – including those who were medication therapy and radiation naïve, those who had responded to SSAs, and those who had received other treatments but were not currently taking SSAs. Not all of these populations correspond to the licensed indication for pegvisomant.

Two meta-analyses[9, 10] and two observational studies [11, 12] assessed the link between IGF-1 and mortality. These meta-analyses did not claim to have carried out a systematic review to identify all relevant studies. They reported using some systematic review methods, such as a database search, but components such as a description of study characteristics and quality assessment of the included studies were not included.

One meta-analysis contained 4,806 participants from 18 observational studies, and was of low quality.[9] A clear and focussed question was provided, however only basic search terms were

used in a single database to identify references, in addition to this the conference abstracts from the US Endocrine Society were hand searched. This analysis did not provide any details of the individual studies, therefore it is difficult to judge whether it was suitable to combine data. No quality assessment was performed for the included studies. The second meta-analysis also searched a single database but with a more extensive list of search terms.[10] References were screened against the pre-specified inclusion and exclusion criteria. Again no details were provided of the characteristics of the individual studies and number of participants in the meta-analysis was not specified. The observational studies included between 442 and 1,512 participants. Due to their design, these studies are at increased risk of bias; however, as only studies with a large sample size were included, this increases reliability but does not remove risk of confounding. The follow up periods of these studies ranged from an average of six to 10 years and findings were in agreement with trends identified in the meta-analyses.

Overall effectiveness of pegvisomant in achieving patient outcomes

The clinical effectiveness of pegvisomant was assessed in four RCTs[3, 5, 6, 8] including a total of 268 people with acromegaly. The RCTs lasted between 12 weeks and one year. Effectiveness was mainly measured in terms of IGF-1 and GH levels. One RCT reported on mortality.[3] One RCT[8] assessed clinical signs and symptoms and two reported quality of life with regard to specific symptoms.[3, 6] The results of the RCTs are summarised in Table 1.

Pegvisomant monotherapy versus placebo

- One RCT including 112 people with a 12 week follow up compared daily doses of pegvisomant (10, 15 and 20mg) versus placebo.[8]
- IGF-1 decreased from baseline in all groups in this RCT. The greatest decline in IGF-1 (62.5%, p value not reported) was observed with a dose of 20mg pegvisomant; this group also had the highest proportion of patients achieving IGF-1 level normalisation (89% compared with 10% in the placebo group ($p<0.001$) and 54% and 81% for 10mg and 15mg dosage respectively).
- When compared with placebo, pegvisomant-treated participants had significantly increased GH levels from baseline (mean +/- SE: PEG 11.2 +/- 2.4 vs placebo 0.0 +/- 2.2, $p=0.0013$).[7] Another report of this trial examined different doses and found that, when compared to placebo, the change in GH levels from baseline with pegvisomant was significantly higher for those receiving 15mg or 20mg per day ($p<0.001$ compared to placebo), but not 10mg per day.[8]
- A questionnaire designed to evaluate five symptoms and signs of acromegaly, with scores ranging from 0 (no symptoms) to 8 (severe, incapacitating symptoms) was used to assess study participants' clinical state at baseline and 12 weeks.[8] It was not clear whether the questionnaire was validated or if completed by the participant or healthcare professional. Scores for ring size, soft tissue swelling and excessive perspiration all improved significantly for the groups on 15mg and 20mg of pegvisomant but not for the 10mg group, compared with placebo; overall signs and symptoms scores and fatigue scores improved in all three pegvisomant dosage groups compared with placebo.
- Musculoskeletal outcomes were assessed in the same study population but reported separately.[2] At baseline, the bone turnover biomarkers were above the normal limit for osteocalcin (in 23% of participants), serum procollagen 1 carboxy-terminal propeptide (PICP) (19%) and N-telopeptide (NTx) (32%). A significant decrease in these markers was observed in the pegvisomant group (osteocalcin $p=0.009$, PICP $p=0.022$, NTX $p=0.024$). For people treated with pegvisomant there was a significant, positive correlation with changes in PICP levels, however there was no correlation observed for osteocalcin and NTx.

Pegvisomant monotherapy versus active comparators

- One large RCT of 118 treatment naïve adults with acromegaly compared the use of pegvisomant versus long-acting octreotide (an SSA).[3]
- This primary endpoint of this RCT was IGF-1 normalisation at week 52 and participants were stratified by country and severity levels according to IGF-1 upper limit of normal (ULN) levels. The study also aimed to assess dose optimisation.
- There was no significant difference in the proportion of people achieving IGF-1 normalisation with pegvisomant and octreotide. However, the absolute reduction in IGF-1 level from baseline was greater with pegvisomant than octreotide after 24 and 52 weeks (53% (SD 26.3) vs – 42% (SD 28.7), p=0.04) and (–55% (SD 32.9) vs –43% (SD 30.3), p=0.04, respectively).
- In a secondary subgroup analysis of patients with baseline IGF-1 at least twice the upper limit of normal, a higher rate of IGF-1 normalisation with pegvisomant (52%) was observed compared with long-acting octreotide (31%) (p=0.05).
- This RCT investigated mortality as a secondary outcome and reported one death in each of the pegvisomant (2%) and octreotide (2%) groups.[3] The deaths were not considered to be treatment-related.
- Quality of life was measured using the ACROQoL tool which found an improvement in quality of life from baseline in both treatment and comparator groups but the difference between groups was not significant (mean change from baseline PEG 8.5 (SD 16.7), octreotide 6.8 (SD 13.7), p>0.05)[3]

Pegvisomant combination therapy versus SSA monotherapy

- Two small RCTs (n=18 and n=20) assessed the effects of pegvisomant combined with SSAs.[5, 6]
- The first RCT was in 18 people with acromegaly currently well controlled on SSA monotherapy, and assessed whether continuing SSA monotherapy at current dose or reducing SSA dose and adding low dose pegvisomant would be of greater benefit.[5] After a follow up of 24 weeks, it was found that the addition of pegvisomant reduced serum IGF-1 levels compared with continuing SSA monotherapy alone but this reduction was not statistically significant.
- The second RCT[6] added pegvisomant (40 mg daily) or placebo to stable SSA therapy. It measured quality of life using disease-specific tools (AcroQOL and PASQ). Using the AcroQoL tool, a significantly greater improvement in overall quality of life from baseline was found with pegvisomant plus SSA compared to placebo plus SSA (change from baseline PEG plus SSA 6.4 +/- 4.25%, placebo plus SSA -1.1 +/- 7.12%, p= 0.008).[6] When looking at the subdomains of the AcroQoL, physical quality of life also improved more with pegvisomant (p=0.002), but no significant difference between groups was seen for psychological quality of life (p=0.185). PASQ scores for and joint pain did not significantly change from baseline, but the pegvisomant group experienced a greater improvement compared to baseline in scores for soft tissue swelling (PEG -0.5 +/- 1.37, placebo 0.0 +/- 1.28, p=0.024), excessive sweating (PEG 0.0 +/- 1.79, placebo 0.5 +/- 0.98, p=0.036) and overall health status (PEG -1.0 +/- 1.99, placebo 0.5 +/- 1.36, p = 0.035). PASQ scores were not significantly different between groups from baseline for headache (p= 0.899), fatigue (p= 0.662), or numbness or tingling of the extremities (p=0.175). No differences were found between groups using the (non-disease specific) EQ5D measure of quality of life.

Table 1: Effectiveness of pegvisomant in people with acromegaly

Study	Patients	Intervention	Comparator	Outcomes
Pegvisomant monotherapy versus placebo				
Trainer 2000[8] RCT (double-blind) United States	112 adults (mean age 48 +/- 14 years) with acromegaly **Previous treatment** 93 surgery 57 surgery and radiation therapy 6 radiation therapy only 9 drug therapy 4 no therapy Patients who had received a long-acting somatostatin analogue within 12 weeks before enrolment were excluded.	Pegvisomant (daily) 10 mg (n=26) 15 mg (n=26) 20 mg (n=28)	Placebo (n=32)	**Follow-up: 12 weeks** **Serum IGF-1** % decrease from baseline (ng/ml, +/- SD) Placebo: -4.0% +/- (SD 16.8) 10mg: -26.7% +/- (SD 27.9) 15mg: -50.1% +/- (SD 26.7) 20mg: -62.5% +/- (SD 21.3) **Serum IGF-1** % participants achieving normal levels at any study visit Placebo: 10% 10mg: 54% 15mg: 81% 20mg: 89% p<0.001 for each comparison with placebo **Serum GH** (Mean ng/ml +/- SD) Placebo -0.8 +/- 5.0 10mg 2.7 +/- 5.5 15mg 9.2 +/- 10.6 20mg 14.4 +/- 21.2 Change from baseline compared with placebo was significant in the 15mg (p<0.001) and 20mg (p<0.001) groups. **Scores for signs and symptoms*** Mean change from baseline at 12 week (+/- SD) (p values are for comparison with the placebo group): ***Ring size*** (increments of ring size measured

				using standardised European jeweller's rings, units not further described) Placebo 0.1 +/- 2.3 10mg 0.8 +/- 1.6, p=0.16 15mg 1.9 +/- 2.0, p=0.001 20mg 2.5 +/- 3.3, p<0.001 ***Arthralgia*** . NS difference between placebo and PEG groups at all doses. ***Headache*** NS difference between placebo and PEG groups at all doses. ***Soft-tissue swelling*** Placebo 3+/- 2.3 10mg -0.7+/- 1.6, p=0.12 15mg -1.2+/- 2.3, p=0.05 20mg -1.3+/- 1.3, p<0.001 ***Excessive perspiration*** Placebo +0.1+/- 1.7 10mg -0.6+/- 1.6, p=0.21 15mg -1.1+/- 1.3, p=0.003 20mg -1.7+/- 1.6, p<0.001 ***Fatigue*** Placebo +0.7 +/- 1.5 10mg -0.5 +/- 1.4, p=0.03 15mg 1.3 +/- 1.7, p<0.001 20mg -1.0 +/- 1.6, p<0.001

				Total score Placebo +1.3 +/- 6.0 10mg -2.5 +/- 4.3, p=0.02 15mg -4.4 +/- 5.9, p=0.004 20mg -4.7 +/- 4.7, p<0.001
Fairfield 2002[2] RCT United States (Subset of Trainer 2000 population[8] for whom serum measurements were available)	27 adults with acromegaly (mean age 45 (range 26-66) years	Pegvisomant 10mg (n=7) 15mg (n=6) 20mg (n=7)	Daily subcutaneous injections of placebo (n=7)	**Follow up: 12 weeks** Between group comparison of change from baseline. Mean +/- SD Osteocalcin (PEG -2.20 +/- 0.44 vs placebo 0.01 +/- 0.39 nmol/l, p=0.009) PICP (PEG -23.6 +/- 9.6 vs placebo 18.1 +/- 12.8 µg/l, p=0.022) NTx (PEG -4.4 +/- 1.4 vs placebo 1.0 +/- 0.3nmol/l, p=0.024)
Pegvisomant monotherapy versus active comparator				
Ghigo 2009[3] RCT (open-label, parallel group, dose-optimisation) 50 centres in 13 countries (Australia, Brazil, Canada, France, Germany, Greece, Italy, Ireland, Norway, Spain, Sweden, United Kingdom, and the United States)	118 treatment naïve (no radiotherapy or medical therapy) adults Mean age (Pegvisomant 49.0 (SD 14.0) Octreotide 49.8 (SD 13.8)) with acromegaly. Participants who had surgical resection were required to be ≥2 months post-surgery. Total	Pegvisomant (Medications were to be titrated in order to achieve normal IGF-1 levels.)	Octreotide long-acting release (LAR) (Medications were to be titrated in order to achieve normal IGF-1 levels.)	**Follow-up: 52 weeks.** **Serum IGF-1** % participants achieving normal levels: Pegvisomant 51%Octreotide 34% (p=0.09). Patients with baseline IGF-1 ≥ twice upper limit of normal had a higher rate of IGF-1 normalisation with pegvisomant (52%) than with octreotide LAR (31%)(p=0.05). **Serum GH** Mean (SD): Pegvisomant 32.5 (41.4) ng/ml Octreotide LAR to 6.0 (23.5) ng/ml.

	number who had surgery not reported.			(Significance not reported) **Mortality** Two deaths occurred during the study (one (2%) in each group). Neither was considered treatment-related. **ACROQoL scores** Mean change (SD) from baseline Pegvisomant 8.5 (16.7) vs Octreotide 6.8 (13.7) (p value>0.05, exact value not provided)
Pegvisomant combination therapy				
Neggers 2008[6] RCT (double blind, placebo-controlled, crossover study)	20 adults (median age 56 (range 39-74) years) with acromegaly **Previous treatment** 15 surgery, 6 surgery and radiation therapy, 5 drug therapy All participants were on a stable long-acting monthly SSA treatment for at least 36 months and continued to receive this during the trial.	Pegvisomant 40 mg per week (plus continuing SSA treatment)	Placebo (plus continuing SSA treatment)	**Follow up: 36 weeks** (two 16 week treatment periods separated by a four week washout) **Serum IGF-1** All within the age-adjusted normal range. Quality of life/symptoms/signs (below) all reported as % change from baseline +/- SD. **AcroQoL**** ***Global*** PEG 6.4% +/- 4.25, placebo -1.1% +/- 7.12, p=0.008 ***Physical sub-category*** PEG 8.0% +/- 7.88,placebo 0.0% +/- 6.25, p=0.002 ***Psychological sub-category*** PEG 3.6% +/- 6.09, placebo -0.9% +/- 9.36, p= 0.185 ***Appearance (subdomain of psychological QoL)*** PEG 4.0% +/- 7.97, placebo -2.0% +/- 12.09, p=0.409

				Personal relations PEG 0.0% +/- 6.14, placebo -4.0% +/- 9.66, p=0.109 **PASQ*** Mean change from baseline +/-SD** ***Total*** PEG -2.0 +/- 6.60, placebo 1.5 +/- 5.02, p=0.038 ***Soft tissue swelling*** PEG -0.5 +/- 1.37, placebo 0.0 +/- 1.28, p=0.024 ***Excessive sweating*** PEG 0.0 +/- 1.79, placebo 0.5 +/- 0.98, p= 0.036 ***Overall health status*** PEG -1.0 +/- 1.99, placebo 0.5 +/- 1.36, p=0.035 ***Joint pain*** PEG -1.0 +/- 1.47, placebo 0.0 +/- 1.49, p=0.083 NS improvement reported for the following PASQ domains: headache, fatigue, numbness of tingling of the extremities. Mean change values not reported for these domains.
Madsen 2011[5] RCT (non-blinded, parallel study) Denmark	18 adults (mean age 54 +/- 3 years) with acromegaly **Previous treatment** Surgery n (%) SSA+Peg 9 (75%) SSA 5 (83%) Radiotherapy n (%) SSA+Peg 1 (8%)	Pegvisomant (15–30 mg twice per week) plus SSA (octreotide LAR 6.7–20mg per four weeks or lanreotide Autogel 24–60 mg per four weeks)	Continuing SSA monotherapy (octreotide LAR 10–30 mg per four weeks or lanreotide Autogel 80mg per four weeks)	**Follow-up: 24 weeks** **Serum IGF-1** Change from baseline did not differ significantly between groups. (p=0.15) Mean IGF-1 (24 weeks) SSA 221+/- (SE 17) µg/litre vs Combined 189 +/- (SE 30), p=0.48 **Serum GH** Median (range)

	SSA 1 (17%) Participants were well controlled on SSA monotherapy			Mean Serum GH level (µg/litre) (week 24) Combined 1.47 (0.29 to 3.42) vs SSA 0.44 (0.16 to 2.79), p=0.008 Nadir GH level (week 24) Combined 1.10 (0.26 to 2.45) vs SSA 0.36 (0.07 to 1.61), p= 0.001 p values are between group differences in change from baseline.

Additional drug therapy not reported in all studies. Scores for signs and symptoms based on questionnaire designed to evaluate five symptoms and signs of acromegaly, with scores ranging from 0 (no symptoms) to 8 (severe, incapacitating symptoms). It was not clear whether this was validated or if completed by the participant or healthcare professional.**AcroQoL comprises 22 questions. Each question has five possible answers scored 1–5, with a total maximum score of 110. A score of 110 reflects the best possible QoL. ***PASQ is a disease-specific questionnaire, consisting of six questions on individual signs and symptoms scoring 0–8 and the seventh question addressing the overall health status, based on the other six questions, scoring 0–10. The maximum total score of the six symptom questions is 48, representing the most severe signs and symptoms.*

Evidence of effectiveness in different subgroups of acromegaly patients

Only one RCT directly compared effectiveness of pegvisomant in different subgroups of acromegaly patients.[3] This 52-week, multicentre, open-label, randomised study (summarised in Table 1 above), aimed to see if pegvisomant lowered IGF-1 more than octreotide long-acting release in 118 treatment naïve patients (i.e. who had no prior medical therapy or radiotherapy). . In participants with higher IGF-1 levels at baseline, pegvisomant provided better outcomes than octreotide.

Association between IGF-1 and GH levels and long term mortality in people with acromegaly

Four studies were identified that looked at the association between IGF-1 and GH levels and long term mortality.[9-12]

One meta-analysis[9], including 18 observational studies and two subsequent observational studies[11, 12] performed a statistical analysis to find the standardised mortality ratios (SMRs) overall, and their association with IGF-1 and GH levels. The meta-analysis, which included a large number of patients (n=4,806) found a significantly increased risk of mortality in people with acromegaly overall compared with the general population; this finding was not replicated in the smaller observational studies. When examining SMR by IGF-1 and GH levels, the meta-analysis and one of the subsequent observational studies showed that, for participants with lower levels of IGF-1 or GH, there was no significant difference in mortality risk compared with the general population. However, the meta-analysis found that, when IGF-1 or GH levels are increased above normal in people with acromegaly, the risk of mortality was significantly increased, from a SMR of 1.1 (95%CI 0.9 to 1.4) to 2.5 (95%CI 1.6 to 4.0) for IGF-1 and 1.1 to 1.9 for GH. The larger observational study split participants into those with active and controlled disease and similarly found significantly increased risk of mortality for “active disease” (not defined) and reduced risk when the disease was “under control”.[11] These studies are summarised in Table 2 below.

A meta-analysis from Italy (not described in the table below) combined data from 10 studies and found that people with hormonal evidence of residual disease (based on GH levels) experienced excess mortality compared to those with lower GH levels.[10] It found a Mortality Rate Ratio (the ratio of SMRs for those with higher versus those with lower GH levels) of 1.83 (95% 1.03 to 3.24) in those with GH levels above a 2.5 µg/L cut off compared to those with lower GH levels and 1.72 (95% 0.96 to 3.08) using a 5.0µg/L cut-off.

Table 2: Association between IGF-1 and GH levels and long term mortality

Study	Study type	n	Overall SMR (95% CI)	Elevated IGF-1 SMR	Normalised IGF-1 SMR	Elevated GH SMR	Normalised GH SMR
Holdaway 2008[9]	Meta-analysis	4,806	1.7 (1.5 to 2.0) p<0.00001	2.5 (1.6 to 4.0) p=0.0001	1.1 (0.9 to 1.4) p=0.45	1.9 (1.5 to 2.4) p<0.00001	1.1 (0.9 to 1.4) p=0.50
Mercado 2014[12] Mexico City	Observational	442	0.72 (0.41 to 1.03) NS	0.94 (0.43 to 1.44) NS	0.46 (0.087 to 0.83) S	1.5 (0.42 to 2.48) NS	0.44 (0.16 to 0.72) S
				Active disease SMR**		**Controlled disease SMR****	
Arosio 2012[11] Italy	Observational	1,512	1.13 (0.87* to 1.46) (NS)	1.93 (1.34 to 2.70) (S)		0.59 (0.37 to 0.90) (S)	

*Figure of 0.87 reported in the abstract, and 0.86 reported in main text of this publication.**Definitions were not provided for active or controlled disease.(NS) Non-significant based on CI spanning 1 (i.e. the SMR which would indicate equivalence with the general population); (S) Significant based on CI not spanning 1 (p values not reported)

4.2 Trials in progress

One clinical trial (NCT01538966) is currently in progress (https://clinicaltrials.gov/ct2/show/NCT01538966?term=acromegaly+AND+pegvisomant&rank=6) and was identified through searching www.clinicaltrials.gov on 2nd October 2015.

The open label randomised study is being carried out by the Cedars-Sinai Medical Centre to evaluate whether low dose somatostatin receptor ligand (SRL) combined with pegvisomant, either daily (15-60mg) or weekly (40-120mg) will achieve controlled serum IGF-1 levels, compared to combination high dose SRL and weekly pegvisomant. The investigators state that lower doses of therapy will greatly reduce cost of acromegaly therapy. The estimated number of participants is 51 and completion date of the study is December 2018.

4.3 Evidence of cost effectiveness

e cost effectiveness analysis conducted alongside a systematic review evaluated the cost effectiveness of pegvisomant relative to standard care in a UK setting.[1] A model was used that had been previously constructed by the drug manufacturer to compare pegvisomant treatment with standard care. The model was re-run to estimate a feasible lower limit for the Incremental Cost Effectiveness Ratio (ICER) of pegvisomant compared with standard care (i.e. a best case scenario). The model appeared to compare pegvisomant monotherapy for individuals who are inadequately controlled, compared with long-acting SSA treatment. Costs for drug therapy, scans and laboratory tests were obtained through personal communications, British National Formulary and expert opinions and included in the model and a perfect drug scenario adopted. This showed that over a 20 year period the cost effectiveness of PEG is very unlikely to fall below £80,000 per Quality Adjusted Life Year or £212,000 per Life Year Gained.

The assumptions in this model included a total annual cost for PEG of £30,482 (£100 per 20 mg dose) and for standard care of £15,409. Based on this analysis and assumptions, pegvisomant was considered unlikely to represent good value for money when considered against the current standards typically applied to interventions in the UK National Health Service.

4.4 Safety

The safety of pegvisomant was reported in four randomised controlled trials.[3, 5, 6, 8] Pegvisomant has a number of associated safety concerns and adverse events. The more serious of which are changes to blood sugar levels and liver problems.

A key difference between somatostatin analogs and pegvisomant is the possible different effects on glycaemic control. Changes to blood sugar levels were assessed in three randomised trials.[3, 5, 8] When compared with placebo and SSA combination therapy, pegvisomant did not show any benefit for blood sugar, fasting glucose and insulin.[3, 5, 8] However, when compared with octreotide, fasting glucose levels decreased in both diabetic and non-diabetic participants, and a significant difference was seen between the groups (p=0.0001).[3] As GH causes a decrease in insulin sensitivity, the increase in GH seen with pegvisomant may lead to an increase in glucose tolerance in some people treated with pegvisomant, this may lead to a fall in glucose levels. For this reason people with diabetes treated with pegvisomant should be carefully monitored and doses of anti-diabetic drugs reduced as necessary.[13]

Liver function was assessed in two studies by the presence of the enzymes alanine transaminase (ALT). When compared with octreotide, both treatment groups saw significant hepatic enzyme elevations (more than three times the Upper Level of Normal (ULN)) in four (7%) pegvisomant-treated patients and four (7%) octreotide-treated patients, all of who had normal levels at baseline.[3] As a result of increased liver enzyme levels there were three patients (two in the pegvisomant group and one in the octreotide group) who withdrew and normalised upon treatment discontinuation. When SSA and combined PEG/SSA therapy were compared, elevated liver enzymes were found in two patients in the combined group during the treatment period. Changes in ALT from baseline to week 24 were not significantly different between groups (-0.5 (-7 to 5) (SSA only) vs 5.5 (-5 to 173) (SSA plus pegvisomant), p= 0.06).[4]

Pituitary tumour size was reported in two RCTs,[3, 8] one comparing pegvisomant to placebo[8] and the other comparing it to octreotide.[3] Neither found a significant difference in change in tumour volume between groups from baseline, However, isolated increases in pituitary size are recorded in the studies identified and as pathological reasoning suggests this may occur with raised GH levels post-marketing and registry studies monitoring these adverse events would help quantify any risk if any.

Adverse events were described in two randomised trials.[3, 8] In the Ghigo study, a similar number of adverse events occurred with pegvisomant and octreotide.[3] The proportion of people having treatment-related adverse events was higher in the octreotide group (51% octreotide vs 38% pegvisomant – significance not reported); discontinuation due to these events was higher with pegvisomant, but this difference was reported as not significant (9% vs 4%, p value not reported) when pegvisomant was compared with placebo. Treatment-related adverse events were reported to be mild to moderate in both groups. When pegvisomant was compared with placebo in the Trainer study, the incidence of adverse events was similar across groups.[8]

Table 3: Summary of safety findings of included studies

Study	Patients	Intervention	Comparator	Outcomes
Pegvisomant monotherapy versus placebo				
Trainer 2000[8] RCT (double-blind) United States	112 adults (mean age 48 +/- 14 years) with acromegaly **Previous treatment** 93 surgery 57 surgery and radiation therapy 6 radiation therapy only 9 drug therapy 4 no therapy Patients who had received a long-acting somatostatin analogue within 12 weeks before enrolment were excluded.	Pegvisomant (daily) 10 mg (n=26) 15 mg (n=26) 20 mg (n=28)	Placebo (n=32)	**Follow-up: 12 weeks** Adverse events that occurred in at least 10% of participants n (%) **Upper respiratory tract infection** Placebo n=5 (16%) 10mg n=5 (19%) 15mg n=4 (15%) 20mg n=5 (18%) **Headache** Placebo n=4 (12%) 10mg n=3 (12%) 15mg n=2 (8%) 20mg n=3 (11%) **Injection-site reaction** Placebo n=0 10mg n=2 (8%) 15mg n=1 (4%) 20mg n=3 (11%) **Pain (scalp, neck, shoulders arms and legs)** Placebo n=2 (6%) 10mg n=2 (8%) 15mg n=1 (4%) 20mg n=4 (14%) **Diarrhoea** Placebo n=1 (3%) 10mg n=1 (4%) 15mg n=0 20mg n=4 (14%)

				Nausea Placebo n=1 (3%) 10mg n=0 15mg n=2 (8%) 20mg n=4 (14%) **Flatulence** Placebo n=0 10mg n=0 15mg n=1 (4%) 20mg n=3 (11%)
Sesmilo 2002[7] RCT United States (Part of Trainer 2000 population)	26 people with acromegaly	Pegvisomant (daily) 20 mg (n=12)	Placebo (n=14)	**Follow up: 12 weeks** **20mg dose** No differences, compared with placebo, were found in levels of: • Homocysteine • IL-6 • lipoprotein(a) • insulin • glucose • triglyceride • cholesterol (total, LDL, and HDL) • insulin resistance index IRHOMA.
Pegvisomant monotherapy versus active comparator				
Ghigo 2009[3] RCT (open-label, parallel group, dose-optimisation) 50 centres in 13 countries (Australia, Brazil, Canada, France, Germany,	118 treatment naïve (no radiotherapy or medical therapy) adults (pegvisomant 49.0 (SD 14.0) Octreotide	Pegvisomant (Medications were to be titrated in order to achieve normal IGF-1 levels.)	Octreotide LAR (Medications were to be titrated in order to achieve normal IGF-1 levels)	**Follow-up: 52 weeks** **Adverse events (AE)** Pegvisomant – 44 AEs reported Octreotide LAR – 48 AEs reported Treatment-related AE occurred in 21 (38%) and 29 patients (51%) respectively (p values not reported). Discontinuation due to treatment related AE occurred in 5 patients (9%) with pegvisomant, and 2 (4%) with octreotide (p values not reported). **Tumour volume**

Greece, Italy, Ireland, Norway, Spain, Sweden, United Kingdom, and the United States)	49.8 (SD13.8) with acromegaly			Change from baseline Mean (SD) Pegvisomant 0.036 cubic centimetre (cc) (SD 0.163); octreotide LAR, –0.355 cc (SD 1.427) (p=0.077).
Pegvisomant combination therapy				
Madsen 2011[5]/ 2012[4] (non-blinded, parallel study) Denmark	18 adults (mean age 54 +/- 3 years) with acromegaly **Previous treatment** Surgery n (%): SSA+Peg: 9 (75%) SSA: 5 (83%) Radiotherapy n (%) SSA+Peg:1 (8%) SSA: 1 (17%) Participants were well controlled on SSA monotherapy	Pegvisomant (15–30 mg twice per week) plus SSA (6.7–20mg per four weeks) or lanreotide Autogel (SSA) (from 24–60 mg per four weeks)	SSA monotherapy (octreotide long-acting release (10–30 mg per 4 wk) or lanreotide Autogel (SSA) 80.0 mg per 4 wk)	**Follow-up: 24 weeks** **Liver function[4]** ALT (liver enzymes) change from baseline to week 24 was not significantly different (SSA+PEG 5.5 U/L (range 5 to 173) vs SSA only 0.5 U/L (range -7 to 5),p= 0.06). **Glucose intolerance[5]** **Fasting glucose (mmol/litre**) Median (range) Week 0 SSA+Peg 5.9 (4.9 to 7.3) SSA 5.6 (4.2 to 6.0) Week 24 SSA+Peg 5.7 (4.8 to 8.5) SSA 5.2 (3.7 to 6.2) p=0.75 **2-h glucose (mmol/litre**) Median (range) Week 0 SSA+Peg 8.6 (4.8 to 18.7) SSA 6.8 (5.3 to 11.1) Week 24 SSA+Peg 9.3 (4.3 to 20.5) SSA 7.3 (5.9 to 12.5) p=0.92 **AUC Glucose (area under the curve, units not specified)** Median (range) Week 0 SSA+Peg 1134 (804 to 1933), SSA 1061 (915 to 1130) Week 24 SSA+Peg 1077 (722 to 1963), SSA 910 (787 to 1424), p=0.27 p value is for between-group differences in change from baseline to week 24

Additional drug therapy not reported in all studies.

4.5 Summary of section

One systematic review, two meta-analyses, seven reports of four randomised controlled trials and two observational studies met the inclusion criteria and were conducted predominantly in the US and Europe. The systematic review was well conducted but was used in this report for cost effectiveness information only since it combined a heterogeneity of study types and provided limited information on outcomes from a single RCT[1]. The RCTs ranged in sample size from 18 to 118 and were of good to moderate quality. Two RCTs provided power calculations;[3, 6] two were double-blinded and one stated that assignment to the treatment group was concealed; none indicated how the randomisation sequence was generated.

Two trials compared pegvisomant with placebo and found that a higher proportion of patients achieved normal IGF-1 levels on pegvisomant than on placebo.[3, 5] IGF-1 normalisation was not significantly different between groups on pegvisomant compared with those on the SSA octreotide, but the reduction in IGF-1 from baseline was significantly improved with pegvisomant after 24 weeks (– 53% (26.3 SD) vs – 42% (28.7 SD), p=0.04) and 52 weeks (– 55% (32.9 SD) vs – 43% (30.3 SD), p=0.04)].[3] Pegvisomant combination therapy was compared with SSA monotherapy where no significant difference was found between the groups with respect to IGF-1 levels.[5]

A meta-analysis of observational studies showed that near normal IGF-1 and GH levels were associated with reduced mortality.[9] The standardised mortality ratio (SMR) was 1.1, (95% confidence interval (CI) 0.9 to 1.4) for those with GH levels less than 2.5 µg/L compared with an SMR of 1.9 (95% CI 1.5–2.4) for those with final GH more than 2.5 µg/L. Similarly, a normal serum IGF-1 for age and sex at last follow-up after treatment was associated with an SMR of 1.1 (95% CI 0.9 to 1.4) compared with an SMR of 2.5 (95% CI 1.6–4.0) for those with continued IGF-1 elevation.

When compared with placebo, pegvisomant-treated participants had significantly increased GH levels from baseline. The study also examined different doses and found the change in GH levels from baseline was significant for those receiving 15mg or 20mg per day. [8]

A small number of deaths were reported but none of these were considered to be related to pegvisomant. [3]

Changes to blood sugar levels were assessed in three RCTs.[3, 5, 8] When compared with placebo pegvisomant monotherapy did not show any significant difference in blood sugar, fasting glucose or insulin levels.[8] A similar outcome was seen for pegvisomant combination therapy compared to SSA where no difference was seen for glucose levels.[5] However, when compared with octreotide, mean fasting glucose levels decreased significantly more with pegvisomant in both diabetic and non-diabetic participants (overall p=0.0001).[3]

Liver function was assessed by the presence of the enzymes alanine transaminase (ALT). When compared with octreotide, both treatment groups saw significant hepatic enzyme elevations (more than three times upper limit of normal in four (7%) pegvisomant-treated patients and four (7%) octreotide-treated patients); all had normal levels at baseline. [3]

Pituitary tumour size was reported in a two RCTs.[3, 8] No difference in tumour volume was found between groups from baseline.

Musculoskeletal outcomes were assessed in one study. [2] At baseline the bone turnover biomarkers were above the normal limit for osteocalcin (23%), PICP (19%) and NTx (32%). A significant decrease in these markers was observed in the pegvisomant group.

One study[8] assessed clinical signs and symptoms via questionnaire and found that, after 12 weeks, total and fatigue scores improved in all three pegvisomant dosage groups (10mg, 15mg, 20mg) compared with placebo; scores for ring size, soft tissue swelling and excessive perspiration improved significantly compared with placebo for those on 15mg and 20mg pegvisomant but not 10mg. In a second study[6] of pegvisomant versus placebo in which both treatment groups were on continuing SSAs, an improvement in AcroQOL global and physical quality of life was observed; however no improvement was seen for psychological quality of life. The PASQ showed a benefit for soft tissue swelling, excessive sweating and overall health status, no differences were found using the EQ5D and the groups were otherwise comparable. A greater improvement in ACROQoL was seen from baseline in a study comparing with pegvisomant with octreotide; however, there was no significant difference between treatment and comparator groups.[3]

The incidence of adverse events and discontinuations was similar between groups in a trial that directly compared SSA therapy (octreotide) with pegvisomant[3] and also in a placebo controlled trial.[8]

Based on the analysis and assumptions used in the cost effectiveness model, pegvisomant was considered unlikely to represent good value for money when considered against the current standards typically applied to interventions in the UK National Health Service.

5 Discussion and conclusions

Clinical effectiveness of pegvisomant

1. a) What is the clinical effectiveness of pegvisomant in achieving the patient outcomes of interest in patients with acromegaly?

Four RCTs assessed the clinical effectiveness of pegvisomant[3, 5, 6, 8]. They included a total of 268 people with acromegaly followed up for between 12 weeks and one year. Effectiveness was mainly measured in terms of IGF-1 and GH levels. One RCT reported on mortality;[3] a second[8] assessed clinical symptoms and a third reported quality of life with regard to specific symptoms.[6]

One RCT has shown that pegvisomant is effective in normalising IGF-1 levels in patients with acromegaly compared to placebo.[8] In a mixed population where over 50% had had previous medical therapy, and when used as monotherapy, pegvisomant 20mg daily normalised IGF-1 levels in 89% of patients compared with 10% in the placebo group at 12 weeks ($p<0.001$). This was the primary outcome of a well conducted single, large multicentre randomised controlled trial.[8] The trial included 112 participants with baseline levels of IGF-1 at least 1.3 times normal. The researchers reported few details on randomisation or blinding, but there was adequate follow up to 12 weeks. This trial has a low risk of bias and was the landmark trial on which marketing approval for pegvisomant was granted. The population is not strictly the population group (patients after failure of SSA therapy or intolerant of SSA) for whom this drug is indicated. In the group randomised to 20mg pegvisomant, 21 out of 28 (75%) had received somatostatin therapy and because of the inclusion criteria can be thought of as those without adequate control.

IGF-1 normalisation has been studied in one other randomised controlled trial that compared pegvisomant directly with a long-acting SSA in titrated doses.[3] In this open label study, 118 participants naïve to radiation and medical therapy were randomised. The study was not blinded because of the nature of the titration regime and allocation concealment and method of randomisation are not reported. At 52 weeks follow up, 51% achieved normal IGF-1 levels on a

titrated dose of pegvisomant compared to 34% of patients randomised to a titrated dose of long-acting octreotide, an SSA, difference not significant (p=0.09). This suggested a trend only. A secondary analysis stratified by severity (IGF-1 levels at baseline) found that patients with twice or more the upper limit of normal compared to those who had less than this at baseline, had a significantly greater normalisation at one year (52% with pegvisomant compared with 31% with long-acting octreotide (p=0.05 for the difference).

No significant changes in IGF-1 levels were recorded in a small trial of combination therapy lasting 16 weeks including 20 participants who had all been taking a long-acting SSA for at least three years.[6] The researchers compared a combination of SSA and a weekly pegvisomant injection of 40mg to SSA therapy alone in a randomised controlled crossover trial. The trial was powered to look at improvements in quality of life and symptom scores in people with acromegaly. It found that physical symptoms improved significantly (measured by the AcroQol) and that soft tissue swelling (one measure in the PASQ) also improved significantly in the dual therapy phase of the trial.

Growth hormone (GH) levels in patients receiving pegvisomant increased significantly in one trial in line with its mode of action.[8] However, a concern that this might lead to increasing pituitary size is not born out in the randomised controlled trials reported here. Further registry studies and post-marketing trials might provide further information on this.

These major trials and subsequent smaller, secondary analyses of these have found that the benefits attributable to normalised IGF-1 levels are associated with other improvements. Among the patients treated with 15 mg or 20 mg of pegvisomant daily in one RCT, ring size, soft-tissue swelling and excessive perspiration scores had improved at 12 weeks compared with placebo. In the same study, fatigue scores and overall scores for signs and symptoms also improved across all pegvisomant groups (10mg, 15mg, 20mg) compared with placebo.[8] Similar improvements in overall quality of life and physical signs/symptoms were shown in a second RCT comparing pegvisomant with placebo in which all patients were on continuing SSA therapy.[2] However, a third study comparing pegvisomant with octreotide, showed an improvement in AcroQOL scores from baseline in both groups, but the difference between groups was not significant.[3]

Musculoskeletal outcomes were assessed in one randomised study.[2] At baseline the bone turnover biomarkers were above the normal limit for osteocalcin (23%), PICP (19%) and NTx (32%). A significant decrease in these markers was observed in the pegvisomant group. The clinical significance of this finding was not reported.

Many people with acromegaly have diabetes or glucose intolerance and so the effect of pegvisomant on markers of glucose metabolism or blood glucose has been of interest and studied in three trials. In a head to head trial of pegvisomant combination therapy versus long-acting SSA in people who were already well controlled on SSA monotherapy, no significant difference in fasting glucose or two hour levels was found.[5] In a direct comparison between SSA and pegvisomant mean fasting glucose decreased in diabetic and non-diabetic patients on pegvisomant whereas octreotide LAR was associated with an increase at week 52 (p=0.005 and p=0.003 between groups, respectively).[3] When compared with placebo pegvisomant monotherapy did not show any significant difference in blood sugar, fasting glucose or insulin levels. The product characteristics recommend that the dosage of diabetic medication in people with diabetes treated with pegvisomant is monitored.[13]

No evidence was found relating to other outcomes of interest such as the effect of pegvisomant on co-morbidities associated with, acromegaly.

b) Is there evidence that pegvisomant is more effective in some patient subgroups than others?

There is moderate level evidence from a secondary analysis of data from one RCT of 118 patients naïve to radiation or medical therapy that pegvisomant may be more effective than a long-acting SSA in patients with more severe disease (i.e. higher IGF-1 levels) at baseline.[3]

The sub groups of patients not responding adequately to SSA therapies have been tested in two of the trials identified and reported above (see question 1(a)).[3, 8]

Patients already controlled on SSA therapies were investigated in two further trials[6] looking at quality of life reported above (see question 1(a)) and a study of combination therapy looking to see if those patients well controlled on SSA can be successfully transferred to a reduced dose of SSA and low dose pegvisomant.[5]

The Madsen trial included 18 acromegalic patients and was reported as a randomised parallel group study, though few details were recorded regarding the process of randomisation, allocation concealment or blinding.[5] Patients, with a mean age of 54 years, were well controlled on SSA monotherapy, and randomised to unchanged SSA monotherapy or combination treatment with pegvisomant (15–30 mg twice a week) and SSA (half the usual dosage). It measured quality of life using the EQ5D and PASQ alongside measures of glucose metabolism and found that, although combination therapy maintained IGF-1 levels, it did not provide significant additional benefits for patients over 24 weeks.

c) In people treated for acromegaly how strongly are IGF1 and GH measurements associated with long term mortality?

Two meta-analyses of observational studies and two subsequent observational studies identified have confirmed an association between IGF1 and GH measurements with long term mortality.[9-12] This has been shown by an significant elevation in the standardised mortality ratio (SMR) a measure that compares the rates of observed mortality rates in acromegalic patients with the expected rates in a healthy population, standardised for the differences in age and sex between populations. Healthy populations have a SMR of 1.0. In these cohort or registry studies, people with acromegaly were treated in a variety of ways, but a meta-analysis shows that a near normal IGF-1 (or GH level) is associated with reduced mortality (SMR 2.5 in the elevated normalised IGF-1 group and 1.1 in the normalised IGF-1 group).[9] The studies in the meta-analyses date back to 1970. There has been an improvement in mortality for the treated condition over time and the analyses are also subject to some confounding from a lack of randomisation. However, in the largest meta-analysis, there is a significant trend for studies that report higher than 70% rates of normalisation to show reduced mortality.[9] The results suggest that a normal serum IGF-I level in people with acromegaly is associated with near normal mortality.

2. What is the safety and tolerability of pegvisomant in terms of:

a) Liver dysfunction

We found two studies which assessed liver function by the presence of the enzyme alanine transaminase (ALT). In one, a randomised comparison of pegvisomant with octreotide, both treatment groups saw significant hepatic enzyme elevations (more than three times the Upper Level of Normal (ULN)) in a similar proportion of patients (four (7%) on pegvisomant and four (7%) on octreotide), all of who had normal levels at baseline.[3] As a result of increased liver enzyme levels, three patients (two on pegvisomant and one on octreotide) withdrew from treatment; their ALT levels normalised on treatment discontinuation.

There was some indication of increased risk of liver dysfunction with pegvisomant combination treatment in a small secondary publication of 18 patients treated with reduced doses of SSA and pegvisomant,[4] but the difference was not significant. Long term post-marketing studies might add further data and it is noted that the product characteristics recommend caution in prescribing pegvisomant if baseline liver tests are elevated.[13]

b) Pituitary tumour growth

In two RCTs, pituitary tumour size was not found to be significantly different with pegvisomant therapy when compared to placebo[8] or octreotide[3], at least in the short term. Long term registry or post-marketing studies should continue to monitor this potential adverse effect reported in the literature.

c) Other side effects?

Pegvisomant has a number of associated safety concerns and adverse events, the more serious of which are changes to blood sugar levels (see question 1(a)) and liver problems (see question 2(a)).

Adverse events were described in two randomised trials.[3, 8] A similar number of adverse events occurred with pegvisomant and the SSA octreotide.[3] The proportion of people having treatment-related adverse events was higher with the octreotide group (51% vs 38%); discontinuation due to these events was higher with pegvisomant but this difference was not significant (9% vs 4%, p value not reported) when pegvisomant was compared with placebo.[8] Treatment-related adverse events were reported to be mild to moderate in both groups. When compared with placebo the incidence of adverse events was similar across groups. [8]

Another RCT (n=118) reported on mortality and found no difference between pegvisomant monotherapy and SSA (octreotide) over one year in those who were radiation and medication therapy naïve (one death (2%) in each group).[3] The deaths were not thought to be treatment-related.

3. How cost effective is pegvisomant in:

a) patients with acromegaly who remain inadequately controlled with conventional therapy (monotherapy) compared to alternatives or no treatment?

Cost effectiveness has not been widely reported, however the cost effectiveness of pegvisomant relative to standard care was assessed in one UK based analysis, using 2009 assumptions.[1] The model was based on the pegvisomant drug manufacturer's model, and appeared to compare pegvisomant monotherapy for individuals who are inadequately controlled, compared with long-acting SSA treatment. The assumptions in this model included a total annual cost for PEG of £30,482 (£100 per 20 mg dose) and for standard care of £15,409.

The model found that over a 20 year time horizon the cost effectiveness of PEG is very unlikely to fall below £80,000/QALY or £212,000/LYG.
The study concluded that pegvisomant is unlikely to represent good value for money when considered against the current standards applied to interventions in the UK Health service. No other cost effectiveness comparisons were identified, e.g. for combination therapy.

b) patients with acromegaly who remain on dopamine agonists or somatostatin analogues (SSAs) (combination therapy) compared to alternatives or no treatment?

We did not identify any studies to answer this question.

4. Supplementary questions

a) At what stage in the course of the disease would patients most benefit from using pegvisomant, as either monotherapy or combination therapy, to treat their acromegaly?

The implication from the secondary analysis of data by Ghigo suggests that people with more severe disease, defined as IGF-1 levels more than twice the upper limit of normal, benefit more from pegvisomant than those with lower IGF-1 levels.[3]

b) Which patient groups would most benefit from the use of combination therapy (i.e. pegvisomant with SSA)?

The literature did not provide any direct evidence on whether particular groups of patients would benefit from the use of combination therapy, for example pegvisomant with SSA. However, it is noted that in the head to head trial of pegvisomant versus SSA therapy, pegvisomant did reduce mean fasting glucose further than SSA in diabetic and non-diabetic patients. This suggests that special consideration might be given to patients with poorly controlled diabetes; however, further studies of this are needed.[3]

c) If there is optimal dose of pegvisomant as a monotherapy?

A number of studies trialled different daily doses of pegvisomant as a monotherapy. In a placebo controlled trial, a daily dose of 20mg resulted in the best rates of IGF-1 normalisation.[8] In the same study, questionnaire scores for clinical signs and symptoms were more consistently improved for participants on 15mg and 20mg pegvisomant when compared with placebo than for participants on 10mg pegvisomant.

d) If there is an optimal dose of pegvisomant as a combination therapy?

Different doses of pegvisomant in combination therapies were not tested against each other. One trial did use reduced doses of pegvisomant in combination therapy with half dose SSA therapy.[5] Pegvisomant at a dose of 15–30 mg twice per week plus SSA (6.7–20mg octreotide per four weeks or 24–60 mg lanreotide Autogel per four weeks) maintained IGF-1 at 24 weeks with no significant differences between the two groups. Although this was a small study, it suggests that it may be possible to use lower doses of pegvisomant which would be cheaper than full doses in combination therapies. This hypothesis will need further testing and is being addressed in an RCT due for completion in December 2018.

Competing Interest

All SPH authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from NHS England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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7 Search Strategy

The PICOS table below was used to guide the search. The criteria used to select evidence for inclusion are described in Section 4.1.

P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	**1.** Patients with acromegaly where existing first and second line therapies (surgery, radiotherapy, other medical treatments (somatostatin analogues and dopamine agonists)) have failed to reduce disease activity or those intolerant of other treatment. 2. Treatment naïve patients
I – Intervention Which intervention, treatment or approach should be used?	Pegvisomant Combination therapy (Pegvisomant and a somatostatin analogue or dopamine agonist)
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Somatostatin analogues Dopamine agonists Transphenoidal Surgery Radiotherapy Placebo
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* Clinical effectiveness including: Mortality Clinical symptoms and/or active complications of acromegaly (e.g. sleep apnoea. glucose intolerance, impaired systolic or diastolic cardiac function, osteoarthritis) Control or amelioration of co-morbidities of acromegaly such as: - Hypertension - Glucose intolerance/diabetes mellitus

	- Cardiac hypertrophy, systolic and diastolic function - Colonic polyps - Musculoskeletal function and arthritis Elevated age-sex related IGF-1 Elevated basal GH and elevated nadir GH during a standard GH/OGTT Safety and adverse effects Side effects and toxicity, including liver dysfunction and pituitary growth Quality of life measures such as body image, mood, pain, energy, strength, ability to undertake activities, relationships etc *Important to decision-making:* Cost effectiveness

Assumptions / limits applied to search

Inclusion criteria

- Articles published between January 1995 and August 2015
- Articles in the English language
- Articles reporting findings on the research questions listed
- Systematic reviews
- Randomised control trials
- Controlled studies
- Cohort studies

Exclusion criteria

- Studies with findings of sample reported in a more recent publication.

- Case Series
- Abstracts, posters, conference reports

Embase.com (MEDLINE & Embase)

#1 'acromegaly'/de
#2 acromegal*:ab,ti OR akromegalia:ab,ti OR megalakria:ab,ti
#3 #1 OR #2
#4 'pegvisomant'/de
#5 pegvisomant:ab,ti
#6 #4 OR #5
#7 #3 AND #6 AND [english]/lim AND [1995-2015]/py

Cochrane Library (CDSR, CENTRAL, HTA, NHS EED, DARE)

#1 acromegal*:ti,ab,kw
#2 MeSH descriptor: [Acromegaly] this term only
#3 pegvisomant:ti,ab,kw
#4 #1 or #2
#5 #3 and #4

Additional search for Acromegaly AND mortality AND IGF/GH levels
1. (acromegal*[tiab] OR acromegaly[mh])
2. (mortality[Title) OR mortality[MeSH Terms]
3. 1 AND 2
4. "Acromegaly/mortality"[Mesh]
5. 3 OR 4
6. "insulin like growth factor i"[MeSH Terms]
7. "growth hormone"[MeSH Terms]
8. (IGF-1[Title/Abstract] OR IGF-1[Title/Abstract] OR “Insulin-Like Growth Factor I”[Title/Abstract] OR GH[Title/Abstract] OR "growth hormone"[Title/Abstract])
9. 6 OR 7 OR 8
10. 5 AND 9
11. 5 AND 9 Filters: Publication date from 1995/01/01 to 2015/12/31; English