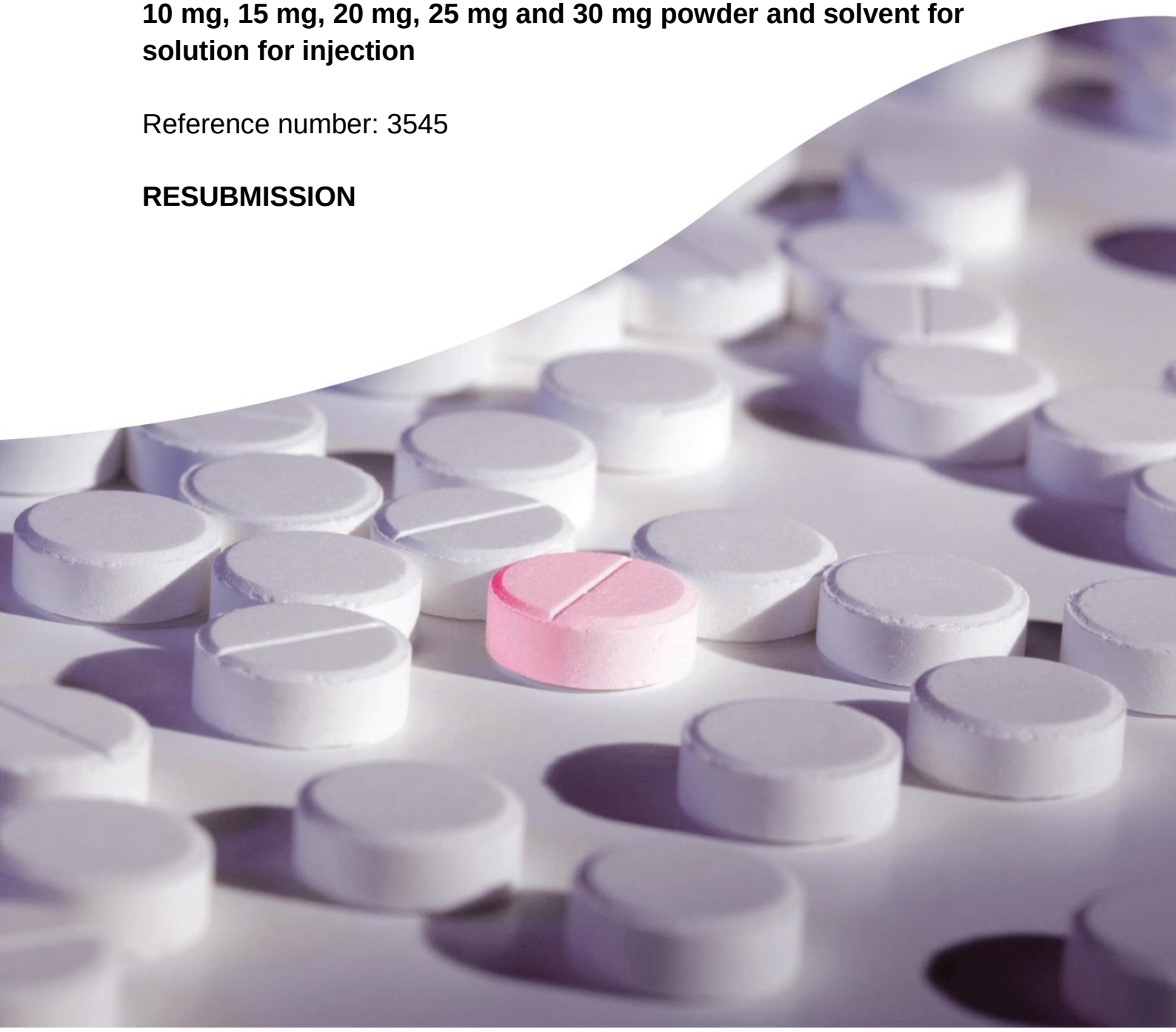
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Pegvisomant (Somavert®)
10 mg, 15 mg, 20 mg, 25 mg and 30 mg powder and solvent for solution for injection

Reference number: 3545

RESUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Pegvisomant (Somavert®) 10 mg, 15 mg, 20 mg, 25 mg and 30 mg powder and solvent for solution for injection

This assessment report is based on evidence submitted by Pfizer Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Pegvisomant (Somavert®) is indicated for the treatment of adult patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalise insulin-like growth factor-1 (IGF-1) concentrations or was not tolerated[2].
Dosing	A loading dose of 80 mg pegvisomant should be administered subcutaneously under medical supervision. Following this, pegvisomant 10 mg reconstituted in 1 ml of solvent should be administered once daily as a subcutaneous injection. Dose adjustments should be based on serum IGF-1 levels. Serum IGF-1 concentrations should be measured every four to six weeks and appropriate dose adjustments made in increments of 5 mg/day in order to maintain the serum IGF-1 concentration within the age-adjusted normal range and to maintain an optimal therapeutic response. The maximum dose should not exceed 30 mg/day. Refer to the Summary of Product Characteristics (SPC) for further dosing information[2].
Marketing authorisation date	13 November 2002[3]

2.0 DECISION CONTEXT

2.1 Background

Pegvisomant was appraised and not recommended for use by the All Wales Medicines Strategy Group (AWMSG) in June 2005[4] and October 2013 as the case for cost-effectiveness had not been proven[5]. Since this time, AWMSG has recommended the use of pasireotide (Signifor®) as an option for the treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue (SSAs)[6]. The company has provided a resubmission for pegvisomant that includes new clinical evidence for pasireotide as the comparator, as well as updated cost-effectiveness evidence and a Wales Patient Access Scheme (WPAS).

Acromegaly is a rare, progressive debilitating disorder caused by hypersecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1)[7,8]. In > 99% of people, acromegaly is caused by a GH-secreting, benign pituitary tumour (adenoma)[7]. Clinical manifestations of acromegaly include physical, metabolic and local changes[7]. People with acromegaly have a shortened life expectancy and a two to three times increase in

mortality[7]. Factors contributing to increased mortality include: higher prevalence of hypertension, hyperglycaemia or diabetes, cardiovascular disease, cardiomyopathy and sleep apnoea[7].

In the majority of patients, first-line treatment will be tumour excision[6]. Radiotherapy can also be given as first-line treatment, or second-line following surgery[8]. Medical therapy is used for people with acromegaly where surgery or radiotherapy is ineffective or inappropriate[8]. Current medical therapies include SSAs like pasireotide, dopamine agonists and GH antagonists[4,5]. However, a proportion of people with acromegaly do not achieve biochemical control with the treatment options that are currently available. Clinical expert opinion sought by AWTTC indicates that pasireotide is used as a last-line option. Pegvisomant, a GH-receptor antagonist, works by binding to GH-receptors on cell surfaces, preventing GH from binding, therefore stopping intracellular GH signal transduction and production of IGF-1[8].

2.2 Comparators

The comparator included in the company submission is pasireotide (Signifor®)[1].

2.3 Guidance and related advice

- NHS England. Clinical Commissioning Policy: Pegvisomant for acromegaly as a third-line treatment (2016)[7].
- The Endocrine Society. Acromegaly: An Endocrine Society clinical practice guideline (2014)[9].
- The Acromegaly Consensus Group. A consensus on the diagnosis and treatment of acromegaly complications (2013)[10].
- American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for the diagnosis and treatment of acromegaly – 2011 update (2011)[11].
- The Acromegaly Consensus Group. A consensus on criteria for cure of acromegaly (2010)[12].
- The Acromegaly Consensus Group. Guidelines for acromegaly management: An update (2009)[13].

AWMSG has previously issued a non-recommendation for the use of pegvisomant (Somavert®) in 2005[4] and 2013[5]. AWMSG issued a recommendation for pasireotide (Signifor®) in 2016[6].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submitted two pivotal clinical studies: SEN-3614, a phase III study that used the dosing regimen on which the licence was granted, and SEN-3611, a phase II study that used once weekly off-label dosing[1]. The company submission also includes extension studies from these pivotal studies (SEN-3615 and SEN-3613A, respectively, which both used the licensed dosing) and an observational study (ACROstudy). In addition, new evidence was submitted, which includes an indirect treatment comparison for pegvisomant versus pasireotide[1].

3.1 SEN-3614

SEN-3614 was a double-blind, placebo-controlled, fixed-dose phase III study designed to test the efficacy and safety of once-daily pegvisomant as 10 mg, 15 mg and 20 mg doses, in patients with acromegaly[8,14]. Patients (≥ 18 years of age) were included in the study if they had IGF-1 levels ≥ 30% above the upper limit of the normal range. The study took place over a 12 week period at centres across the EU and US. A total of 112 patients were entered into the study; 93 patients (83%) had undergone pituitary surgery, 57 patients (51%) had received surgery and radiation therapy, and 81 patients (72%) had received prior SSA therapy[14]. Patients who had received long-acting SSAs in the previous 12 weeks were not eligible[8,14]. Patients were randomised to four treatment groups: placebo or pegvisomant in 10 mg, 15 mg or 20 mg doses[14].

The primary endpoint was percent reduction in IGF-1 concentrations at week 12 compared to baseline[8,14]. The mean percentage change in IGF-1 concentrations was significantly higher than placebo in all pegvisomant treatment groups, and was dose related (Table 1). IGF-1 levels normalised at 12 weeks in 64% of patients treated with pegvisomant (all doses), versus 9.7% in the placebo group[8,14]. Secondary endpoints included the mean standard ring size (of the fourth digit, right hand) at 12 weeks, and changes in scores for symptoms and signs of acromegaly at 12 weeks[14]. Overall, there was a significant reduction in ring size for the 15 mg ($p = 0.001$) and 20 mg ($p < 0.001$) treatment groups. There was also a significant improvement in total score for symptoms and signs across all groups treated with pegvisomant, with the biggest difference observed with the 20 mg dose[14].

Table 1. Primary efficacy endpoint of the SEN-3614 study[8,14]

IGF-1 (ng/ml)	Placebo (n = 31)*	Pegvisomant 10 mg (n = 26)	Pegvisomant 15 mg (n = 26)	Pegvisomant 20 mg (n = 28)
Mean	639.7	449.1	320.9	278
Range	148–1,291	89–894	70–878	78–720
Mean % change from baseline	−4.0	−26.7	−50.1	−62.5
p-value (versus placebo)		0.0001	0.0001	0.0001
p-value (versus 10 mg pegvisomant)			0.0048	0.0001
p-value (versus 15 mg pegvisomant)				0.0155

IGF-1: insulin-like growth factor-1; n: number of patients.
*32 patients were enrolled onto the placebo arm: one patient withdrew from the study after five days of treatment due to surgical referral.

3.2 SEN-3611

SEN-3611 was a double-blind, placebo-controlled, phase II study designed to test the efficacy and safety of once-weekly pegvisomant in 30 mg and 80 mg doses[8]. Patients (≥ 18 years of age) were included in the study if they had a diagnosis of acromegaly and had IGF-1 levels ≥ 50% above the upper limit of the normal range[8]. A total of 46 patients entered the study and were allocated to received weekly doses of 30 mg pegvisomant (n = 16), 80 mg pegvisomant (n = 15) or placebo (n = 15). Mean duration of exposure to pegvisomant was 23 weeks, ranging from 0.14–34.3 weeks[8].

IGF-1 values at baseline were comparable between the two groups[8]. The primary efficacy endpoint was the percentage change of IGF-1 levels observed after six weeks of treatment (Table 2). The mean percentage change of IGF-1 was significantly higher than placebo in both of the pegvisomant groups. The difference between the pegvisomant doses was not significant. IGF-1 levels normalised in 12.5% patients treated with 30 mg pegvisomant, 26.7% patients treated with 80 mg pegvisomant and 6.7% in the placebo group[8].

Table 2. Primary efficacy endpoint of the SEN-3611

IGF-1 (ng/ml)	Placebo (n = 15)	Pegvisomant 30 mg (n = 16)	Pegvisomant 80 mg (n = 15)
Mean % change from baseline (SD)	−0.4 (4.8)	−15.7 (4.8)	−31.3 (6.7)
p-value (versus placebo)		0.0426	0.0008
p-value (versus 30 mg pegvisomant)			n.s.
IGF-1: insulin-like growth factor-1; n: number of patients; SD: standard deviation; n.s.: not significant.			

3.3 Extension studies SEN-3613A and SEN-3615

Patients who took part in studies SEN-3611 and SEN-3614 were offered to continue in open-label extension studies SEN-3613A and SEN-3615, respectively[8,15]. In total, 160 patients were included in a pooled analysis for these extension studies: patients were treated for up to 18 months, with a mean treatment duration of 425 days[15]. All patients received 10 mg pegvisomant daily, which was adjusted in 5 mg increments until IGF-1 concentration was normal or a maximum dose of 40 mg was reached[15].

Patients were included in three cohorts based on whether they had completed 6 months (n = 131), 12 months (n = 90) or 18 months (n = 39) of continuous daily pegvisomant treatment at the time of data cut-off[15]. Characteristics were similar across the cohorts, with the exception that IGF-1 concentrations at baseline were substantially higher in the patients who continued treatment for 18 months or more. Mean IGF-1 serum fell by 50% or more in patients treated for 6–18 months ($p < 0.001$). Normal IGF-1 concentration was achieved in 87 of 90 patients (97%) who were treated for 12 months or more[15].

3.4 ACROstudy

ACROstudy is an open-label, global, observational phase IV safety study designed to provide long-term safety data and treatment outcomes in patients with acromegaly treated with pegvisomant as used in routine clinical practice[16]. The previous submission to AWMSG considered an interim analysis of the ACROstudy reporting data on 1,288 patients who received pegvisomant, including as monotherapy and combination therapy[17]. The latest results included 1,867 patients from 14 countries enrolled between 2004 and 2012[16]. To determine the long-term outcomes of pegvisomant alone, only data from the patients receiving pegvisomant monotherapy were assessed (n = 710)[16]. Patients (> 18 years of age) were included in the assessment if they had received at least one dose of pegvisomant as monotherapy, with up to 5 years of follow-up[16].

Nearly all subjects had received other acromegaly therapy prior to pegvisomant: 333 (46.9%) had received surgery and medical therapy, 183 (25.8%) had received surgery, radiation therapy and medical therapy[16]. A total of 611 patients (87.2%) had received other medical therapy prior to the study, of which 63.6% had received SSAs, 33.8% had received both SSAs and dopamine agonists, and 2.6% dopamine agonists only[16]. A total of 37 patients (5.2%) had received no previous treatment[16].

Patients received pegvisomant for a mean of 5.4 years and were followed in the ACROstudy for a mean 3.8 years[16]. Following five years of pegvisomant therapy, 67.5% of patients had achieved normal levels of IGF-1, and 2.6% of patients had IGF-1 levels below the lower limit of the normal range. Patients who were assessed longitudinally (n = 155) received pegvisomant for a mean of 7.5 years (ranging between 1–9.9 years): in this group, 15.5% had normal IGF-1 at baseline (the start of pegvisomant treatment), 63.8% had normal IGF-1 at one year of treatment and 65.8% had normal IGF-1 following five years of treatment. Most patients with normalised IGF-1 levels at baseline or the one

year interval remained normalised at five years. However, variations did occur, including 25 patients who were normalised at year one but became elevated at year five[16].

3.5 Indirect treatment comparison

To address the lack of direct comparative evidence, the company included a systematic review and indirect treatment comparison designed to estimate the relative efficacy and safety of pegvisomant compared to pasireotide[1]. The systematic literature review included interventional studies (phase II to phase IV), randomised controlled studies or single arm studies conducted in adult patients with acromegaly and containing at least one of the interventions (pegvisomant or pasireotide). The primary outcome included was percent suppression in IGF-1 concentrations from baseline. Safety endpoints included adverse events, serious adverse events and discontinuation due to adverse events[1].

Six publications, representing three studies, met the criteria for inclusion[1]. Of these three studies, two were considered relevant for inclusion and one was not included as it was outside the licensed indication for pegvisomant[1]. The only comparable outcome between the two studies (SEN-3614 and POALA) was the normalisation of IGF-1 levels[1]. This outcome was reported at 12 weeks in SEN-3614 and 24 weeks in POALA: for the purposes of the indirect treatment comparison, the efficacy at both endpoints was assumed to be the same. Other outcomes were either not present in both of the studies, or used different definitions. Furthermore, the control arms differed between the two studies: SEN-3614 used placebo, whereas POALA used an active comparator (octreotide or lanreotide). For the purposes of this indirect treatment comparison, the control arms from both studies (placebo and active comparator) were assumed to be equal. Overall, no comparisons between pegvisomant and pasireotide reached statistical significance[1].

3.6 Safety

No comparative safety data are available for pegvisomant and pasireotide, and no comparable safety outcomes were reported from the indirect treatment comparison submitted by the company. Safety data were pooled from the pegvisomant studies: the majority of adverse reactions were mild to moderate in intensity, of limited duration and did not require discontinuation of treatment[2]. The most commonly reported adverse events (≥ 10% of patients) were headache (25%), arthralgia (16%) and diarrhoea (13%)[2]. The most commonly reported adverse events in the pivotal study, SEN-3614, were similar across all study groups, and included upper respiratory tract infection, headache, injection-site reaction and pain (scalp, neck, shoulders, arms and legs)[14].

Post-authorisation safety surveillance was assessed during the ACROstudy. Overall, adverse events were reported in 345 patients (48.6%) and serious adverse events were reported in 133 patients (18.7%): 22 deaths were reported, of which none were considered treatment-related[16]. The most common serious adverse events were pituitary tumour increase or recurrence, metastatic tumour and cardiovascular events. Serious treatment-related adverse events that lead to medicine withdrawal were: two events of pituitary tumour recurrence, one event of increased transaminases and increased hepatic enzymes, and one event of hypersensitivity reaction[16].

3.7 AWTTC critique

- Acromegaly is a rare, serious, debilitating condition. When untreated, it is associated with increased mortality and reduced quality of life. People with uncontrolled acromegaly following surgery and/or radiotherapy have more severe disease; they are highly symptomatic, seriously unwell and at risk of increased mortality. Clinical expert opinion sought by AWTTC highlighted a definite unmet need for a minority of people with acromegaly who remain uncontrolled despite the currently available treatment options. Pegvisomant is licensed as a last-line

medical treatment for this rare disease and is commissioned for use in NHS England[7].

- Age-normalised IGF-1 level is used to define 'control' of acromegaly for all available treatments and is the only parameter used for pegvisomant[9,10]. In the pivotal SEN-3614 study, 82% of patients receiving 20 mg pegvisomant had achieved normal IGF-1 levels at 12 weeks, compared to 10% in the placebo group. Furthermore, a significant overall decrease in total score for symptoms and signs of acromegaly was reported. Normal IGF-1 levels were achieved in the majority of patients across the pegvisomant studies; however, IGF-1 normalisation rate was lower in the observational ACROstudy than in the pivotal studies. The 'normal' IGF-1 range differed across the studies, which could contribute to the variation in normalisation rate[1,16]. The SEN studies classified normalisation as when a patient achieved a single IGF-1 level within the normal range at least once during the entire follow-up period[1,16]. ACROstudy normalisation was assessed on a yearly basis[1,16].
- The previous submissions considered by AWMSG did not include pasireotide as a comparator. Pasireotide has since been recommended as an option for use in Wales for the indication under consideration and clinical opinion sought by AWTTC confirms this is the most appropriate comparator. In this resubmission, the company submitted an indirect treatment comparison to address the lack of direct evidence for pegvisomant versus pasireotide. However, due to many variations in clinical study protocol between the pegvisomant and pasireotide studies, such as differing comparator arms (placebo in SEN-3614, active comparator in POALA), a true indirect comparison could not be made. Therefore, there remains a lack of evidence comparing pegvisomant with an appropriate comparator product.
- Treatment with pegvisomant is overall well established and included in a number of international clinical guidelines. It is generally positioned as a last-line medical treatment. The majority of patients in the clinical studies received pegvisomant as monotherapy[14-16]. The SPC reports that the use of this medicine in combination with other medicinal products for the treatment of acromegaly has not been extensively investigated[2]. Clinical expert opinion sought by AWTTC states that pegvisomant would predominantly be used as monotherapy; however, there may be a minority of patients where pegvisomant may be used in combination with another medicinal treatment such as an SSA. This is also reflected in clinical guidelines. Overall, the results from the observational ACROstudy for pegvisomant combination therapy are consistent with those reported for monotherapy[17].
- Due to a different mechanism of action, pegvisomant differs from other available medicinal products for acromegaly, including pasireotide. For example, as a GH antagonist, pegvisomant prevents IGF-1 production and therefore affects the systemic and metabolic aspects including diabetes and glucose intolerance of acromegaly[8]. Unlike pegvisomant, pasireotide (and other SSAs) bind to somatostatin receptors to suppress GH secretion, and can target pituitary tumour growth as well as the systemic disease[18]. There is also a difference in administration between pegvisomant and pasireotide. Pegvisomant is administered subcutaneously and can be self-adminisered[2], whereas pasireotide is administered by a deep intramuscular injection[19].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost-minimisation analysis (CMA) comparing pegvisomant with pasireotide, as a third-line treatment in adult patients with acromegaly

who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with SSAs did not normalise IGF-1 concentrations.

A simple Markov cohort model, with 12-week cycles, is used to estimate the difference in cost between pegvisomant and pasireotide. The model adopts an NHS Wales Personal Social Services perspective, with a five year time horizon. It is characterised by three health states: uncontrolled acromegaly, controlled acromegaly and death. Patients enter the model without normalised IGF-1 and receive either pegvisomant or pasireotide. Those patients who normalise after the first cycle continue treatment for the duration of the model. Those who fail to normalise at week 12 discontinue treatment and switch to standard care (i.e. continued SSAs or care for co-morbidities only). The normalisation rate used at week 12 is taken from the ACROstudy at year five and is assumed to be equal for both treatments[16]. Mortality risk is assumed to be equal to the age and gender matched Welsh population in patients who are adequately controlled[20]. However, a condition-adjusted mortality ratio of 1.55 is applied to patients in the uncontrolled state, in keeping with the findings of a large retrospective cohort study of over 1000 patients[21].

Costs for treatment are calculated as the sum of the costs of medicine acquisition, medicine administration and monitoring. Pegvisomant is associated with a WPAS; a confidential discounted price has therefore been used in the economic analysis. In contrast, the list price has been used for pasireotide, given that there is no patient access scheme associated with this treatment. Pegvisomant is administered subcutaneously; pasireotide is administered by a deep intramuscular injection. Pegvisomant therapy is initiated with a loading dose of 80 mg. Following this, patients self-administer 10 mg pegvisomant once daily; the dose is then titrated by increments of 5 mg/day in order to maintain IGF-1 concentration within normal range and to maintain optimum therapeutic response. [Commercial in confidence information removed]. The maximum licensed dose for pegvisomant is 30 mg/day. The recommended starting dose for pasireotide is 40 mg every four weeks, which can be increased to 60 mg if patients are not fully controlled after three months. In line with their respective SPCs[2,19], administration costs for pegvisomant consist of one 10 minute consultation with a nurse to administer the loading dose and to be taught how to self administer. For pasireotide, administration costs are accrued when the patient visits a nurse for 10 minutes to receive the injection every four weeks. The frequency of monitoring is guided by SPCs[2,19] European Society Clinical Practice Guidelines[9], and a previous health technology assessment (HTA) for pegvisomant[22]. In keeping with this previous HTA, it is assumed that both treatments require regular endocrinology outpatient attendance every four weeks. Unit costs for the treatments are taken from the Monthly Index of Medical Specialities (MIMS)[23], and administration and monitoring unit costs are derived from NHS Reference Costs and Personal Social Services Research Unit costs[24]. Costs are discounted at a rate of 3.5% per annum.

The submission includes sensitivity and scenario analyses to test the influence of structural and parameter uncertainty on the robustness of the base case results. These explore the impact of: the number of outpatient visits, the percentage of patients achieving IGF-1 normalisation, titration assumptions, unit costs of MRI and ultrasound scans, and maintenance dosing for pegvisomant.

4.1.2 Results

The results of the base case analysis are detailed in Table 3. Treatment with pegvisomant is less costly in the base case as a result of lower acquisition, administration and monitoring costs. In the majority of the sensitivity and scenario analyses conducted, pegvisomant remains the favourable option. All of the univariate sensitivity analyses result in cost savings. However, there are some scenarios where pegvisomant is associated with higher costs than pasireotide. Scenarios are detailed in Table 3.

Table 3. Results of the base case analysis and scenario analyses

Scenario	Costs	Pegvisomant	Pasireotide	Difference	Plausibility
Base case					
Pegvisomant versus pasireotide	Medicine acquisition costs	¶¶	¶¶	¶¶	
	Administration costs	£8	£310	−£302	
	Monitoring costs	£6,625	£6,696	−£71	
	Total costs	¶¶	¶¶	¶¶	
Scenario analyses					
Scenario 1: Alternative life-time time horizon	Medicine acquisition costs	¶¶	¶¶	¶¶	Acromegaly is a life-long condition; a longer time horizon is therefore more appropriate than the limited five year time horizon used in the base case
	Administration costs	¶¶	¶¶	¶¶	
	Monitoring costs	¶¶	¶¶	¶¶	
	Total costs	¶¶	¶¶	¶¶	
Scenario 2: [CIC information removed] and a life-time time horizon	Medicine acquisition costs	¶¶	¶¶	¶¶	[CIC information removed]. This scenario explores the impact of changing the mean dosing assumption, but remains subject to uncertainty.
	Administration costs	£8	£1,171	−£1,163	
	Monitoring costs	£22,957	£22,850	£107	
	Total costs	¶¶	¶¶	¶¶	
Scenario 3: Assumes maintenance dose of 20 mg for pegvisomant and a life-time horizon	Medicine acquisition costs	¶¶	¶¶	¶¶	This scenario explores a more conservative mean dosing assumption for pegvisomant. Again, this scenario remains subject to uncertainty.
	Administration costs	£8	£1,171	−£1,163	
	Monitoring costs	£22,957	£22,850	£107	
	Total costs	¶¶	¶¶	¶¶	

¶¶ Commercial in confidence information removed
CIC: commercial in confidence

4.1.3 AWTTC critique

The reliability of the CMA is dependent on the extent to which pegvisomant is considered to be therapeutically equivalent to pasireotide. The company justifies the use of a CMA, as opposed to a cost-utility analysis (CUA), on the basis that the indirect treatment comparison comparing pegvisomant and pasireotide did not identify a statistically significant difference in IGF-1 normalisation rates. Furthermore, clinical expert opinion sought by the company suggests that efficacy equivalence for pegvisomant and pasireotide is a conservative assumption. The base case results of the CMA indicate that pegvisomant is cost-saving when compared with pasireotide. However, there are a number of limitations that create uncertainty around the appropriateness of the economic evaluation adopted and the findings from the CMA. These limitations are listed below, together with the strengths of the analysis.

Strengths of the economic analysis:

- The model reflects the correct patient population and adopts an appropriate perspective and discount rate. The assumptions and methods applied are transparent.

Limitations of the economic analysis:

- The justification provided for using CMA is not convincing. The AWMSG guidance notes state that economic evaluations should take the form of a CUA, with results expressed as incremental costs per quality-adjusted life-year (QALY) gained. There are some exceptions where CMAs may be acceptable. These include cases where there are no clinically meaningful differences in the distribution of effects between the medicine and its comparator(s). Effects include all dimensions of health, including impact on health-related quality of life, survival, adverse events, patient preference and adherence. This requires well-designed equivalence trials for the evaluation of efficacy (effectiveness) and evidence of close comparability of other effects, which were not the subjects of the equivalence analysis. The company acknowledges the limitations of the indirect treatment comparison conducted. The safety data reported in the SPCs also show differences in adverse events[2,19]. What impact these differences have on cost or utility are uncertain. These heterogeneities highlight that a CUA would be a more suitable approach to the economic evaluation; the CMA is not appropriate in this instance.
- Acromegaly is a life-long condition. However, the base case has a limited time horizon of five years. The company has addressed this by conducting extra analyses to explore the impact of a life-time time horizon. The results from these analyses are detailed in Table 3.
- The acquisition costs in the model are subject to uncertainty, given that the optimum dose of pegvisomant is unknown.
- The model adopts the normalisation rate from the ACROstudy. This is applied at 12 weeks in the model, but is the rate recorded after five years of therapy in the ACROstudy. It is uncertain how valid this rate is at the 12 week stage. This uncertainty also applies to the normalisation rate used for patients receiving pasireotide.
- The CMA compares pegvisomant versus pasireotide as monotherapies. Clinical expert opinion sought by AWTTC confirmed that pegvisomant would predominantly be used as monotherapy; however, there are instances where combination therapy may be considered. The SPC states that the use of pegvisomant in combination with other medicinal products for the treatment of acromegaly has not been extensively investigated, and that it should be considered whether to continue treatment with SSAs[2]. Despite the lack of relevant data, it would have been beneficial to explore this potential by scenario analyses.

4.2 Review of published evidence on cost-effectiveness

A literature search conducted by AWTTC did not identify any cost-minimisation studies comparing pegvisomant with pasireotide as a third-line treatment in adult patients with acromegaly. However, the search did identify two cost-utility analyses: one compared pegvisomant plus SSA with pasireotide in Finland[25] and the other reported the original AWMSG appraisal, comparing pegvisomant versus SSAs[22]. A previous appraisal undertaken by SMC for pegvisomant also included a cost-utility analysis, comparing pegvisomant with SSAs. These findings suggest that a cost-utility analysis has been considered the most appropriate approach in prior economic evaluations of pegvisomant.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company has estimated that there will be 13 people with uncontrolled acromegaly in year 1, increasing to 17 people in year 5. This estimate is based on Welsh Government population statistics[26] and European prevalence data[27]. To calculate the number of patients who require treatment in Wales, the company has combined prevalence estimates and incidence estimates[28], together with a condition-adjusted mortality rate[29] and clinical expert opinion on the proportion of patients likely to have uncontrolled acromegaly[22],' namely 7.5%. An assumed market share of 30% in year 1, increasing to 50% in year 5 is further applied to estimate the number of patients likely to be prescribed pegvisomant in Wales for the indication covered in the submission. This results in four patients in year 1, increasing to eight patients in year 5. Sensitivity analyses have been performed to assess the impact of: market share, the acquisition cost of pegvisomant, the proportion of patients eligible for treatment, and pegvisomant maintenance dose.

5.1.2 Results

The budget impact is presented in Table 4. [Commercial in confidence information removed]. This estimate incorporates cost differences resulting from the displacement of pasireotide. [Commercial in confidence information removed].

Table 4. Company-reported costs associated with use of pegvisomant for the treatment of acromegaly

	Year 1 (2017)	Year 2 (2018)	Year 3 (2019)	Year 4 (2020)	Year 5 (2021)
Number of eligible patients	¶¶	¶¶	¶¶	¶¶	¶¶
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Treated patients	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market without pegvisomant	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market with pegvisomant	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ Commercial in confidence information removed					

[Commercial in confidence information removed].

5.1.3 AWTTC critique

- The submission gives a transparent account of the methods and data sources used to estimate budget impact. The company has also incorporated condition-adjusted mortality risk for the population of interest.
- [Commercial in confidence information removed]. However, the optimum dose of pegvisomant is unknown; this results in uncertainty surrounding net medicine acquisition costs.
- It is uncertain how the estimates for uptake have been calculated, and therefore whether or not they are a realistic forecast. However, the company has explored this uncertainty via sensitivity analyses. Variations of ±20% result in net savings each year and not additional costs.

5.2 Comparative unit costs

Acquisition costs for treatments for acromegaly are given in Table 5.

Table 5. Examples of medicine acquisition costs for third-line treatment of acromegaly

Regimens	Example doses	Approximate costs per patient (per annum)
Pegvisomant (Somavert®)	15 mg once daily by subcutaneous injection 20 mg once daily by subcutaneous injection	£29,250 £36,500
Pasireotide (Signifor®)	40 mg to 60 mg intramuscular injection once every four weeks	£29,900
See relevant Summaries of Product Characteristics (SPC) for full licensed indications and dosing details. Costs are based on MIMS list prices as of August 2017[23]. Costs of administration are not included. This table does not imply therapeutic equivalence of medicines or the stated doses.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, pegvisomant (Somavert®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that pegvisomant (Somavert®) may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 25 July 2017
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

The applicant company suggests that pegvisomant fulfils the AWMSG policy relating to orphan and ultra-orphan medicines, and medicines developed specifically for rare diseases. AWMSG defines an ultra-orphan medicine as a medicine that has been granted European Medicines Agency (EMA) designated orphan status and is used to treat conditions affecting not more than 1 in 50,000 in the UK (or 60 patients in Wales). The definition applies to the full population of the licensed indication[30].

The EMA Committee for Orphan Medicinal Products granted pegvisomant orphan status for the treatment of acromegaly in 2001; however, this status was withdrawn in November 2012, at the end of the market exclusivity period[31]. The company has estimated that there are 13–17 people in Wales meeting the licensed indication; these figures have been confirmed by clinical expert opinion sought by AWTTC.

Pegvisomant is not licensed for any other conditions, and therefore is likely to be used in less than 60 patients in Wales.

Should the New Medicines Group (NMG) and AWMSG consider the policy to apply, additional criteria for appraising the medicine will be considered (see Table 6).

Table 6. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases, considerations for NMG and AWMSG

NMG and AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impact on patients and their carers.	Acromegaly is a chronic condition associated with changes in physical appearance, increased risk of cardiovascular disease and other forms of morbidity, and premature mortality in those who do not respond to current surgical and medical treatment. It is typically diagnosed between the ages of 40–50; diagnosis is often delayed, taking over a decade from disease onset, due to symptoms slowly developing over time[7,8].
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	The company has requested that pegvisomant be considered for patients with acromegaly in line with the licensed indication. Pasireotide may also be a suitable medicine for this group of patients. Clinical expert opinion sought by AWTTC stated that due to the different modes of action, the side effect profile between the two medicines differs.
Whether the medicine can reverse or cure, rather than stabilise the condition	The medicine stabilises acromegaly when clinically effective, but does not cure or reverse the condition.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development	Not applicable.
The innovative nature of the medicine	The company claims that pegvisomant represents an innovative approach to the medical management of acromegaly. The mechanism of action differs from other treatments available, and efficacy is independent of tumour status. The effects of pegvisomant, unlike SSAs or dopamine agonists, are not dependent on the dopamine of somatostatin receptor density of the tumour.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education or function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	This criteria is not applicable as the company has submitted a cost-minimisation analysis not a cost-utility analysis.
Added value to the patient's family (e.g. impact on a carer or family life)	Not applicable.
NMG: New Medicines Group; AWMSG: All Wales Medicines Steering Group; AWTTC: All Wales Therapeutics and Toxicology Centre; SSA: somatostatin analogues; QALY: quality-adjusted life-years.	

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