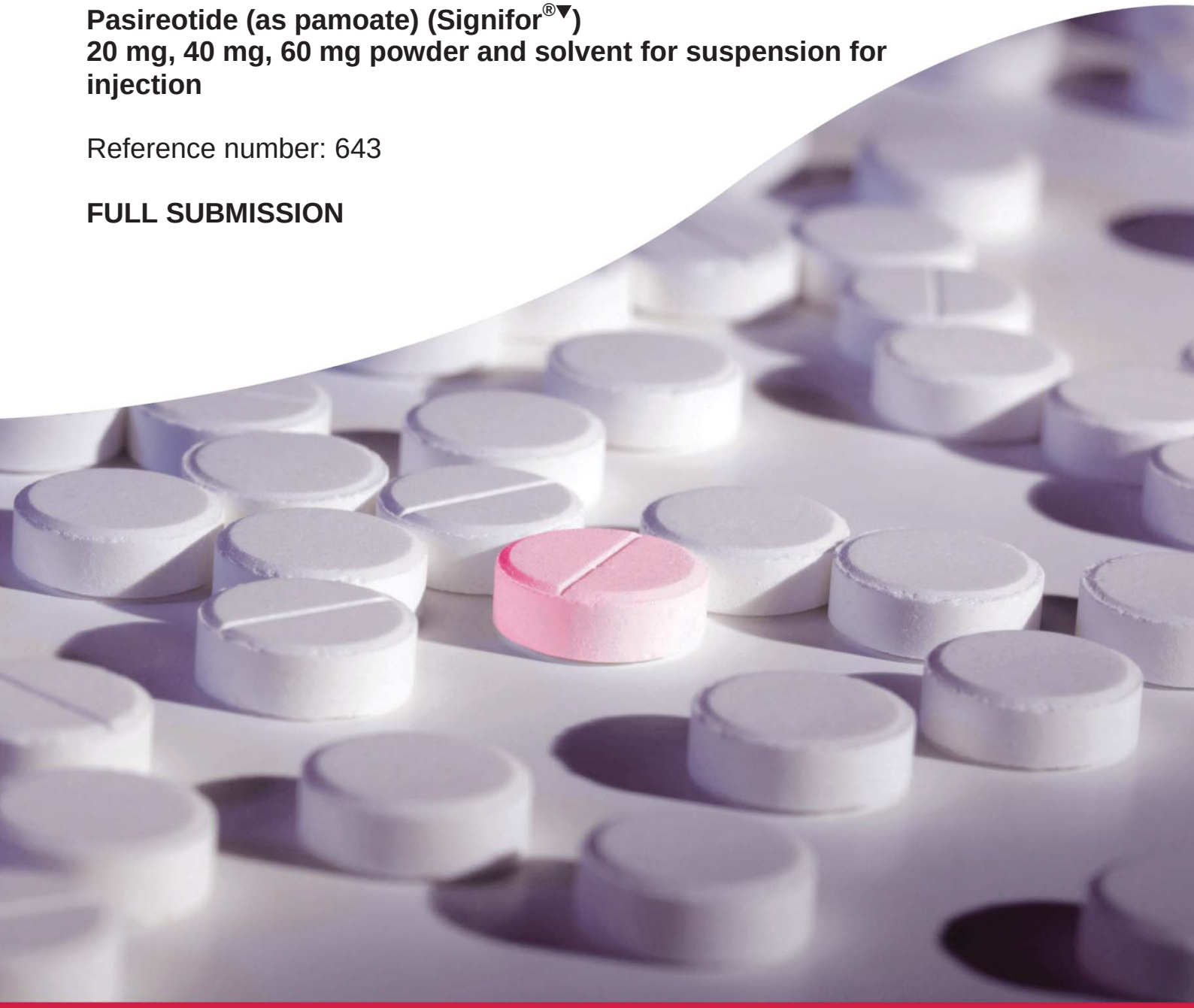
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Pasireotide (as pamoate) (Signifor®▼)
20 mg, 40 mg, 60 mg powder and solvent for suspension for injection

Reference number: 643

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Pasireotide (as pamoate) (Signifor®▼) 20 mg, 40 mg, 60 mg powder and solvent for suspension for injection

This assessment report is based on evidence submitted by Novartis Pharmaceuticals UK Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Pasireotide (as pamoate) (Signifor®▼) 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[2].
Dosing	The recommended initial dose is 40 mg of pasireotide (as pamoate) every 4 weeks. The dose may be increased to a maximum of 60 mg for patients whose growth hormone (GH) and/or insulin-like growth factor-1 (IGF-1) levels are not fully controlled after 3 months of treatment with pasireotide at 40 mg. Pasireotide is to be administered by deep intramuscular injection by a trained healthcare professional. Refer to the Summary of Product Characteristics (SPC) for further information regarding dosing[2].
Marketing authorisation date	19 November 2014 (pasireotide [as diaspartate] subcutaneous formulation was licensed for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed on 24 April 2012)[3].

2.0 DECISION CONTEXT

2.1 Background

Acromegaly is a rare progressive debilitating disorder caused by hypersecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1), in over 95% of patients caused by a GH-secreting, benign pituitary tumour (adenoma)[4,5]. Patients are typically diagnosed from four to more than ten years after onset with the majority of diagnoses occurring in middle age (average age 40 years); men and women are affected equally[4]. Somatic disfigurement causes progressive enlargement of the hands and feet and changes in face shape. Acromegaly also leads to multiple systematic co-morbidity conditions including hypertension, cardiovascular disease, hyperglycaemia, diabetes, osteoporosis, rheumatoid arthritis, sleep apnoea and excessive sweating. Local tumour effects commonly cause headaches and may lead to visual disturbances. Patients with acromegaly have a shortened life expectancy, with a mortality rate that is approximately twice that of the general population, and an average reduction in life expectancy of 10 years[6].

The aim of treatment is to relieve symptoms, to reduce pituitary tumour volume, to avoid tumour relapse, and to reduce mortality to the expected age- and sex-adjusted rates. In the majority of patients first line treatment will be tumour excision[6]. Medical therapy is recommended in patients with persistent disease following surgery or when surgery is not possible or contraindicated[4,5]. Radiotherapy may be used in cases where there is residual tumour mass following surgery and/or if medical therapy is unsuccessful or not tolerated[5].

Current medical therapies include somatostatin analogues (SSAs), dopamine agonists (DAs) and GH antagonists[4,5]. Pasireotide is an SSA and binds to somatostatin receptors (SSTRs), suppressing GH secretion. SSAs are the medical treatment of choice in acromegaly[6]. However, a significant proportion of patients do not achieve biochemical control with currently available treatment options; therefore, there is a significant unmet need for additional, more effective medical treatment[6].

2.2 Comparators

The comparators included in the company submission were the long acting SSAs octreotide (Sandostatin Lar®) and lanreotide (Somatuline Autogel®)[1].

2.3 Guidance and related advice

- The Endocrine Society. Acromegaly: An Endocrine Society clinical practice guideline (2014)[5].
- The Acromegaly Consensus Group. A consensus on the diagnosis and treatment of acromegaly complications (2013)[7].
- American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for the diagnosis and treatment of acromegaly – 2011 update (2011)[8].
- The Acromegaly Consensus Group. A consensus on criteria for cure of acromegaly (2010)[9].
- The Acromegaly Consensus Group. Guidelines for acromegaly management: An update (2009)[10].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a non-recommendation for the use of pegvisomant (Somavert®)[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included evidence from two phase III clinical studies and an indirect treatment comparison (ITC)[1]. Study C2402 evaluated the safety and efficacy of pasireotide long-acting release (LAR) versus octreotide LAR or lanreotide autogel (ATG) in patients with inadequately controlled acromegaly and is described in further detail below. Study C2305 investigated the superiority of pasireotide over octreotide in medically naive patients only and therefore this study will not be discussed in detail[1].

3.1 C2402 (PAOLA) study

This was a multicentre, randomised, phase III study in patients (aged 18 years and older) with inadequately controlled acromegaly (five point, two hour GH concentration > 2.5 micrograms/l and IGF-1 concentration > 1.3 times the upper limit of normal adjusted for age and sex) and who had received octreotide LAR or lanreotide ATG monotherapy for six months or longer[1,12]. Two-thirds of patients had previously received pituitary surgery[12]. Patients (n = 198) were randomly assigned to receive pasireotide LAR 40 mg once every 28 days for 24 weeks (n = 65), pasireotide LAR 60 mg once every 28 days for 24 weeks (n = 65) or continued treatment with octreotide LAR or lanreotide ATG (active control [n = 68]). Patients and investigators were masked to pasireotide dose allocation but not to study medicine assignment[1,12]. After 24 weeks, patients in the pasireotide arms could continue into an ongoing extension phase on blinded treatment if controlled, or start open-label pasireotide LAR 60 mg if uncontrolled[1]. Patients were assessed at week 28 (week 52 for patients continuing treatment). Patients in the active control arm could enter the extension and receive pasireotide LAR 40 mg with a dose increase to 60 mg after three months if they did not achieve control[1].

The primary endpoint was the number of patients achieving biochemical control (mean GH concentration < 2.5 micrograms/l and normalisation of age and sex adjusted IGF-1 concentration) at 24 weeks[1,12]. Biochemical control was achieved by ten (15%) patients in the pasireotide LAR 40 mg group; 13 (20%) patients in the pasireotide LAR 60 mg

group and no patients in the active control group. The absolute difference between the 40 mg group and active control group was 15.4% (95% confidence interval [CI] 7.6–26.5, p = 0.0006) and between the 60 mg group and the active control was 20% (95% CI 11.1–31.8, p = < 0.0001).

The key secondary endpoint was the proportion of patients achieving normalisation of age and sex adjusted IGF-1 at 24 weeks. Other secondary endpoints included GH and IGF levels alone and in combination at 12 and 24 weeks, change in tumour volume and symptoms of acromegaly from baseline at 24 weeks, health-related quality of life (HRQoL), safety and tolerability[1,12]. Selected secondary endpoint results at 24 weeks are shown in Table 1; results at 12 weeks were supportive of those at 24 weeks[1].

Table 1. Selected secondary endpoint results for study C2402 (PAOLA)[6,12,13]

Endpoint	Pasireotide LAR 40 mg (n = 65)	Pasireotide LAR 60 mg (n = 65)	Active control (n = 68)
Proportion of patients achieving normal IGF-1 (sex and age adjusted) at 24 weeks			
% (n)	24.6% (16)	26.2% (26)	0
Absolute difference between treatment group and active control group (95% CI)	24.6% (14.8–36.9) p = 0.0006	26.2% (16.0–38.5) p = < 0.0001	
Proportion of patients achieving GH levels < 2.5 micrograms/l at 24 weeks			
% (n)	35.4% (23)	43.1% (28)	13.2% (9)
Absolute difference between treatment group and active control group (95% CI)	22.1% (6.3–36.6) p = 0.0024	29.8% (12.9–44.2) p = 0.0001	
Proportion of patients achieving a tumour volume reduction of > 25% at 24 weeks			
% (n)	18.5% (12)	10.8% (7)	1.5% (1)
OR versus active control (95% CI for OR)	¶¶	¶¶	
Post hoc analysis of proportion of patients achieving GH levels < 1 microgram/l at 24 weeks			
%	¶¶	¶¶	¶¶
95% CI for OR versus active control	0.95–infinity p = 0.0556	2.06–infinity p = 0.0059	

CI: confidence interval; GH: growth hormone; IGF-1: insulin-like growth factor-1; LAR: long-acting release; OR: odds ratio
¶¶Commercial in confidence data removed

Quality of life (QoL) was measured using the acromegaly QoL questionnaire (AcroQoL); no significant change in QoL was observed[6]. The extension phase of the trial is ongoing; preliminary results are consistent with those in the core phase[1,6].

3.2 ITC

An ITC was conducted to address the absence of direct comparisons between pasireotide LAR and the most commonly used treatments in patients with inadequately controlled acromegaly[1]. Treatments included pegvisomant monotherapy and combination treatment regimens involving pegvisomant, SSAs and DAs (cabergoline and bromocriptine). Systematic literature review identified 19 randomised control trials (RCTs) from which three studies were included in the Bucher fixed-effects ITC[12,14,15], in addition to two reports on a Spanish observational study (ACROCOMB)[16,17]. The efficacy outcome included in the ITC analysis was IGF-1 normalisation only, no significant differences were demonstrated between pasireotide LAR 40 mg and 60 mg and alternative treatments, i.e. pegvisomant monotherapy, pegvisomant in combination with SSAs, cabergoline in combination with SSAs[1].

3.3 Safety

From study C2402, a total of 191 patients were included in the safety analysis. Adverse events (AEs) suspected of being related to study treatment occurred most frequently in the pasireotide LAR 40 mg and 60 mg treatment arms (71.4% and 74.2% respectively); fewer AEs related to study treatment were reported in the active control arm (43.9%)[1,12]. Hyperglycaemia-related AEs were more frequent and of greater severity in the pasireotide treatment arms: 66.7% and 61.3% in the pasireotide LAR 40 mg and 60 mg respectively, and 30.3% in the active control group[1,18]. Antidiabetic medication was initiated in 38% and 39% of patients in the pasireotide LAR 40 mg and 60 mg groups respectively, and in 6% of patients in the active control group[12].

Diarrhoea-related AEs related to study treatment were also higher in the pasireotide LAR groups than in the active control group. No diarrhoea-related AEs related to study treatment were graded 3 or 4[1,18]. The next most common AEs related to study treatment were gallbladder and biliary-related, with similar frequency in all three treatment arms[1].

A total of six patients discontinued treatment due to AEs, five of which were considered to be related to the study treatment[12]. Four of the patients were in the pasireotide LAR 60 mg group (one case of diabetes and three cases of hyperglycaemia) and one in the pasireotide LAR 40 mg group (hyperglycaemia)[12].

Further safety data are available from the phase III study, C2305 (medically naive patients), and additional supportive (dose finding) studies. With the exception of hyperglycaemia AEs, no gross differences were observed in the safety profile between the different populations with regards to common AEs[6]. The Committee for Medicinal Products for Human Use (CHMP) considered the overall safety profile of pasireotide to be acceptable for patients inadequately controlled with other treatments and, with the exception to hyperglycaemia, to be comparable to that of octreotide and lanreotide[6].

3.4 AWTTC critique

- Acromegaly is a rare, serious, debilitating condition and, untreated, is associated with increased mortality and reduced QoL. The clinical manifestations result from peripheral actions of GH and IGF-1 and local tumour mass effect[6]. The majority of patients undergo transphenoidal surgery; those who are unsuitable or do not achieve biochemical control are usually treated with an SSA. Radiotherapy is usually reserved for refractory cases. Clinical expert opinion sought by AWTTC highlighted a definite unmet need for a minority of patients who remain uncontrolled despite currently available treatment options.
- Pasireotide is a second-generation SSA licensed for use in patients inadequately controlled with another SSA. It is stated to have a broader SSTR binding profile than the current predominant therapeutic treatment options, first-generation SSAs octreotide and lanreotide, with high affinity to four of the five receptors (SSTRs 1, 2, 3 and 5)[6]. Other medical treatment options for treating patients with acromegaly include a DA or pegvisomant (Somavert®). Current guidelines suggest a DA as an option in patients with modest disease, or in combination with SSA for those inadequately controlled on an SSA alone. Pegvisomant is also considered an option for those inadequately controlled on a SSA; however, it should be noted that pegvisomant is not recommended for use within NHS Wales[11]. Prescribing data and clinical expert opinion sought by AWTTC demonstrates that pegvisomant (Somavert®) is not in use within NHS Wales for the indication under consideration.
- In study C2402, superiority of pasireotide LAR 40 mg and 60 mg was demonstrated over octreotide or lanreotide active controls for the primary endpoint of biochemical control (GH < 2.5 micrograms/l and IGF-1 normalisation) as defined in the study protocol[12]. In addition, the proportions of

patients with a greater than 25% reduction in tumour volume were significantly greater in both pasireotide arms compared to the active control[13].

- No significant changes in acromegaly symptoms or overall HRQoL were observed in study C2402[6]. In addition, biological control was defined as a level of GH < 2.5 micrograms/l and normalised IGF-1 levels[12], however, new, stricter guidelines define biochemical control to be achieved with a cut off of GH < 1.0 micrograms/l and IGF-1 normalisation[5,9]. Post hoc analysis, using the stricter criteria, obtained a statistically significant difference with pasireotide LAR 60 mg versus active comparator, but not with pasireotide LAR 40 mg (see Table 1)[6]. However, the company highlight that the post hoc analysis was not pre-specified and hence not powered to detect statistical significance in the stricter definition of biochemical response.
- The results of the ITC showed no significant difference between pasireotide LAR and alternative treatments; however, there were a number of limitations in the analysis. In the absence of a common control arm between studies, similarity was assumed between placebo in the pegvisomant study[14] and the active control arm of study C2402[1,12]. As pegvisomant does not affect GH levels, biochemical control could only be compared using IGF-1 levels: this was the only measure of efficacy analysed in the ITC[1]. The company highlighted the heterogeneity between study population characteristics and study design, and the resultant limited robustness of the comparison[1]. Consequently, results of the ITC should be interpreted with caution.
- The AEs associated with pasireotide were similar to those found with other SSAs with the exception of hyperglycaemia which, in comparison, was more frequent and severe[1,12]. CHMP considered hyperglycaemia/diabetes to be easily monitored and managed with standard diabetes medicines[6]. However, it was determined that inducing hyperglycaemia/diabetes in medically naive patients is not acceptable and other SSAs should be tried first in patients with acromegaly. The approved indication was therefore restricted to patients inadequately controlled with other treatments[6].
- CHMP conclude that the long-term effect of treatment in patients inadequately controlled on other SSAs is still lacking. However, interim results from the extension phase of study C2402 indicate that the effect of pasireotide is also maintained over time in this population[6].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) of pasireotide as a second-line SSA compared against continued use of first-line octreotide or lanreotide in the treatment of acromegaly in patients for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with first-line SSA[1]. Pegvisomant, and combination therapy with DA plus a SSA are considered as treatment options only in those who do not have an adequate response to pasireotide or continued first-line SSA, and so are not considered as comparators to pasireotide.

A Markov model, consisting of ten health states has been developed. Patients enter the model with inadequate biochemical control on their SSA (defined by mean GH levels > 2.5 micrograms/l and lack of normalisation of IGF-1) and receive pasireotide or continued SSA. Treatment response is determined at six-month intervals. Those achieving full biochemical response are assumed to remain on pasireotide or continue SSA in the long term, and those with inadequate response move to subsequent treatment with pegvisomant or DA plus SSA (assumed 50:50 in the base case analysis). Inadequate response to these agents is followed by radiotherapy, then a post-radiotherapy state where those who achieve adequate biochemical control remain

without further treatment. Mortality is modelled using Welsh life-tables, adjusted by published standardised mortality ratios to reflect higher risk of mortality for those patients who fail to achieve biochemical control over time[19].

Efficacy is modelled by the probabilities of achieving biochemical control of GH and IGF-1. For pasireotide and the comparator SSA, the probabilities were estimated from 24-week data from the C2402 study (see Section 3.1). For subsequent treatment with pegvisomant or DA plus SSA, the probabilities of achieving control were derived from Bucher ITCs of data from the C2402 trial of pasireotide, two pegvisomant trials[14,15], and retrospective observational studies of DA plus SSA[16,17]. The company has acknowledged many limitations to these ITCs (see Sections 3.2 and 3.4). Probabilities of control with radiotherapy are reported to be based on data from the UK Acromegaly Register.

Medicine acquisition costs for pasireotide and the comparator SSA are based on British National Formulary list prices, with doses as observed in the C2402 trial[20]. Other resource use and costs include healthcare professional costs to administer monthly injections, radiotherapy costs, and ongoing monitoring costs informed by expert opinion. The model incorporates hyperglycaemia/diabetes as a temporary AE for pasireotide and the comparator SSA, based on rates observed in trial C2402, and also the occurrence of a range of comorbidities based on response to treatment, estimated from company data on file (not verified), which are costed using a wide range of assumptions and (unrelated) published estimates. Utility values for weighting health states (e.g. adequate or inadequate control states) are derived from the AcroQOL data collected in the C2402 trial. These are assumed to capture HRQoL associated with acromegaly and the co-morbidities, but a further decrement is applied for diabetes, based on a published catalogue of EQ-5D scores[21].

The base case model adopts a lifetime (up to 55 years) horizon of analysis, with costs and outcomes accrued beyond one year discounted at a rate of 3.5% per annum[1].

4.1.2 Results

The results of the base case analysis, assuming pegvisomant or SSA plus DA in the ratio 50:50 following inadequate response to pasireotide or the comparator SSA, are presented in Table 2. The results suggest pasireotide provides a gain of 0.48 quality-adjusted life-years (QALYs) at an additional cost of £17,880 over the comparator SSA across the modelled lifetime, resulting in a base case incremental cost-effectiveness ratio (ICER) of £37,200 per QALY gained.

Table 2. Results of the base case analysis.

	Pasireotide	SSA	Difference
Total costs (£)	873,696	855,809	17,887
Total life-years	19.58	19.27	0.31
Total QALYs	14.14	13.66	0.48
ICER (£/QALY gained)	**£37,207**		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; SSA: somatostatin analogue.

Probabilistic sensitivity analyses indicated the probability of the ICER being $\leq$ £30,000 per QALY gained was around 9%; the probability of the base case deterministic ICER was < 25%. Scenario analyses and one-way sensitivity analyses in which the base case ICER estimates varied substantially from the base deterministic ICER are presented in Table 3.

Table 3. Results of key sensitivity and scenario analyses.

Scenarios	ICER (£/QALY)	Plausibility
Base case	**£37,207**	Compares pasireotide against continued use of SSA monotherapy only, which has 0% probability of providing full biochemical control as defined. If the rate of response to SSA is increased to 5% this increases the ICER to £101,856 per QALY gained. However, the company deem this an implausible scenario, given the label for paseriotide and that no SSA patients achieved biochemical response in the C2402 study. Assumes long-term ongoing treatment benefits in those who achieve response in the first six months; however, long term data for pasireotide are lacking. Defines GH response (alone or as a component of full biochemical response) as GH < 2.5 micrograms/l, which is assumed to have a SMR of 1.0 (i.e. no elevated risk of death); however, the published source of SMR estimates used in the model notes evidence of an increased mortality in those with GH > 1 microgram/l[19]. No analyses have been provided to explore the cost effectiveness of pasireotide using this stricter definition of GH response or biochemical control. Assumes risks of diabetes with pasireotide are temporary, which is not known, and the assumed utility value attached to diabetes is not explored. Possible bias in impact of AEs in favour of pasireotide. Model is highly dependent on efficacy and costs of subsequent medical treatments, which are subject to very high levels of uncertainty and limitations, being based on the weak indirect treatment comparisons. Sensitivity analyses conducted by the company reveals that when probability of response to pegvisomant is altered to 10% and 56%, the ICERs generated are £32,447 and £50,362 per QALY gained respectively. Similarly, when the probability of response to SSA+DA is changed to 10% and 62%, this yields ICERs of £35,778 and £58,716 per QALY respectively. Model assumes 50% use of pegvisomant and 50% use of SSA plus DA for treatment following failure of pasireotide and the comparator SSA, but pegvisomant is not recommended by AWMSG for use in NHS Wales and its inclusion in the analyses significantly reduces the ICER estimates (see scenario analysis below). Model is highly dependent on inclusion of co-morbidity costs, which are based on company data on co-morbidity rates that have not been verified. All patients undergoing radiotherapy are assumed to remain on medical treatment, and fewer patients on pasireotide are modelled to progress to radiotherapy, this could possibly bias the model in favour of pasireotide. However, the company justify this approach using the results of a small survey conducted with 11 UK acromegaly specialists (1 from Wales), where 7 of the 11 participants reported that > 80% of patients would remain on medical therapy. A scenario analysis assuming 80% of patients who undergo radiotherapy remain on medical treatment increases the ICER to £43,171 per QALY, demonstrating the sensitivity of the model to assumptions on subsequent treatment.
Probability of biochemical response with pasireotide	**60 mg (0.10 to 0.30): £51,379 to £29,286** **40 mg (0.07 to 0.24): £48,377 to £30,168**	Basis of range explored not defined. ICER reliant on probability of pasireotide inducing biochemical response (while assuming SSA confers no benefit).

Scenarios	ICER (£/QALY)	Plausibility
Exclusion of co-morbidity costs	**£86,088**	Demonstrates the reliance of the ICER estimate on co-morbidity costs, which are based on several sources including company data on file that have not been verified.
Utility value for biochemical control varied 0.63 to 0.94	**Pasireotide dominated to £17,080**	Demonstrates model is sensitive to assumed utility value for biochemical control. Utility values for control based on regression analysis and mapping of HRQoL data collected in the C2402 trial, which are subject to uncertainty as the trial observed no significant differences in quality of life based on limited available data. Basis of range explored in sensitivity analysis is not described.
Starting age; 40-65 years	**£33,421 to £61,853**	Demonstrates reliance of base case ICER on discounting of costs and assumed accrual of QALYs over long term.
Subsequent treatment 100% SSA + DA	**£105,489**	As pegvisomant is not recommended for use by AWMSG, this analysis may be more plausible than the base case, which assumes 50% of patients receive subsequent treatment with pegvisomant.
Subsequent treatment 100% Pegvisomant	**Pasireotide dominant over SSA**	Unlikely scenario given pegvisomant is not recommended for use by AWMSG.
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; DA: dopamine antagonist; GH: growth hormone; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; IGF-1: insulin like growth factor-1; QALY: quality-adjusted life-year; SMR: standardised mortality ratios; SSA: somatostatin analogue		

4.1.3 AWTTC critique

The company has compared pasireotide against continued treatment with SSA only, which may exclude other important comparators. The model assumes long-term ongoing treatment benefits in those who achieve biochemical response in the first six months, and temporary impacts of important adverse effects of pasireotide. However, long term efficacy and safety data for pasireotide to support these assumptions are lacking. The ICER estimates are heavily dependent upon the assumed subsequent lines of therapy and their efficacy, which are subject to high levels of uncertainty and may introduce bias in favour of pasireotide. Collectively, the modelled estimates of cost-effectiveness of pasireotide are highly uncertain, and scenario analyses demonstrate that ICERs considerably greater than that reported in the base case analysis may be plausible.

The company states that pasireotide meets the AWMSG criteria for ultra-orphan medicine status (see Section 6.5).

Strengths of the economic evidence:

- The company has made efforts to model the clinical pathway and treatment of acromegaly with pasireotide in the context of limited short term data. Direct comparative data for pasireotide and SSA have been used.

Limitations of the economic evidence:

- The analyses are limited to comparison of pasireotide against continued SSA treatment. Other potential comparators in patients who have had inadequate response are not considered.
- The model assumes long-term ongoing treatment benefits in those who achieve response in the first six months, and temporary impacts of diabetes induced by pasireotide; however, long term efficacy and safety data for pasireotide to support these assumptions are lacking.
- The model is driven by probabilities of biochemical response defined by normalisation of IGF-1 levels and achievement of GH < 2.5 micrograms/l. Any benefit of partial response to continued SSA is not considered, and analyses indicate that the model is very sensitive to assumptions of SSA response. No

analyses are provided using the stricter definition of GH < 1.0 micrograms/l, for which pasireotide 40 mg showed no significant improvement over SSA in the C2402 trial.

- There are several other important sources of uncertainty and potential bias in favour of pasireotide within the model:
    - ICER estimates are heavily influenced by the assumed subsequent treatment with pegvisomant or SSA plus DA, which are modelled using data that are subject to significant uncertainties, and should be interpreted with extreme caution.
    - It is assumed that 50% of patients requiring subsequent treatment will receive pegvisomant, which is not recommended for use by AWMSG. Removal of pegvisomant as a treatment option (in line with AWMSG recommendations against its use) almost triples the ICER estimate to around £105,000 per QALY. Of note, and in contrast to the CUA, the budget impact analysis does not consider displacement of pegvisomant by pasireotide.
    - The benefits of radiotherapy, given last-line in the model, appear to have been estimated incorrectly and would bias the model in favour of pasireotide.
- Sensitivity analyses demonstrate the heavy reliance of the ICER estimates on co-morbidity costs, which are driven by unverified company data on file. Probabilistic sensitivity analyses suggest the probability of pasireotide having an ICER of £37,207 as in the base case deterministic analysis would be less than 25%. The PSA is a function of the input parameters, and would not necessarily account for the bias in the model described above.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published cost-effectiveness analyses of pasireotide in the treatment of acromegaly of relevance to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on a prevalence estimate from an Orphanet report, 2015[22], which the company suggests is in line with Welsh clinical expert opinion, the company estimates there are 60 cases of acromegaly per million population in Wales, equivalent to 185 cases. Using published sources it further estimates there to be around 9 incident cases per year over the next 5 years. An overall standardised mortality rate of 1.7 is assumed for biochemically uncontrolled patients, which are assumed to account for 45% of patients, resulting in a mortality rate of 1.2%[19].

Based on a range of sources and assumptions the company estimates that, of 87 patients assumed to be treated with SSAs, 39 (45%) fail to achieve adequate control and are eligible for pasireotide, equivalent to 21.22% of all acromegaly patients. The company anticipates an uptake of 5% in year 1, rising to 16% in year 5, due to displacement of octreotide and lanreotide in the ratio 75%:25%.

5.1.2 Results

The company's estimates of the net cost of pasireotide to NHS Wales are summarised in Table 4. Two patients are estimated to be treated with pasireotide in year 1 at a net cost of £35,011, rising to 8 patients at a net cost of £132,807 in year 5.

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

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	41	43	44	46	48
Uptake (%)	5%	8%	10%	12%	16%
Treated patients	2	3	4	6	8
Net costs	**£35,011**	**£58,605**	**£76,505**	**£95,706**	**£132,807**

The company has also provided alternative estimates, reported to be based on clinical expert opinion of numbers of eligible patients in Wales, and assuming market share of 10% in year 1, rising to 50% in year 5. Results are presented in Table 5.

Table 5. Alternative budget impact estimate associated with use of pasireotide for the treatment of acromegaly.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	16	16	17	18	18
Uptake (%)	10%	20%	30%	40%	50%
Treated patients	2	3	5	7	9
Net costs	**£26,761**	**£55,993**	**£87,715**	**£121,921**	**£158,611**

5.1.3 AWTTC critique

- The company quotes published figures and expert opinion on the number of patients with acromegaly in Wales (60 per million); however, published estimates vary widely, with the European Medicines Agency (EMA) orphan designation for pasireotide reporting a prevalence as high as 1.2 per 10,000 population in the EU[23]. Eligible patient numbers are therefore subject to uncertainty.
- The estimation of eligible patient numbers are essentially based on company assumptions. The alternative estimates reported to be based on clinical expert opinion are markedly different to those of the company.
- The magnitude of the net cost estimates are similar, highlighting the uncertainty in potential use and costs.

5.2 Comparative unit costs

The Endocrine Society/European Society for Endocrinology published clinical guidelines for the treatment of acromegaly in 2014. Transsphenoidal surgery is recommended as the primary therapy, but for those who do not achieve a surgical cure, medical therapy with SSAs or pegvisomant is suggested for patients with moderate to severe disease, and DA therapy in patients with milder disease[5]. Pasireotide is an SSA, licensed for use in acromegaly in patients inadequately controlled on other SSAs. Example acquisition costs are presented in Table 6.

Table 6. Example costs of pasireotide and potential comparators in the treatment of acromegaly.

Medicines	Example maintenance regimen	Annual cost of maintenance treatment
Pasireotide (Signifor®▼)	40 mg to 60 mg IM injection once every 4 weeks	£29,900
Lanreotide (Somatuline® Autogel®)	60 mg to 120 mg SC injection once every 4 weeks	£7,163 to £12,181
Octreotide (Sandostatin LAR®)	20 mg to 30 mg IM injection once every 4 weeks	£10,089 to £12,915
Pegvisomant (Somavert®)	10 mg to 30 mg SC injection daily (following 80 mg loading dose)	£18,250 to £54,750 (excluding loading dose)
IM: intra-muscular; SC: subcutaneous Costs based on BNF list prices, 18/09/2015[20]. See SPCs for full dosing details[2,24–26]. This table does not imply therapeutic equivalence of medicines or doses.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

AWTTC is of the opinion that, if recommended, pasireotide (Signifor®▼) may be appropriate for prescribing within NHS Wales for the indication under consideration with a shared care agreement.

6.2 Ongoing studies

The company submission highlighted two ongoing studies that are likely to be available within 6–12 months[1]. The 28 week extension phase of study C2402 has an estimated completion date of December 2015. Study C2305, which has not been discussed in this report, has a 12 month cross-over extension phase due for completion in October 2015[1].

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: 07 September 2015
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 pasireotide fulfils the AWMSG criteria for consideration as an ultra-orphan medicine. The current AWMSG policy for appraising orphan, ultra-orphan and rare-disease medicines defines an ultra-orphan medicine as a medicine that has been granted EMA designated orphan status and is used to treat a condition with a prevalence of 1 in 50,000 or less in the UK (or 60 patients in Wales)[27]. This definition applies to the full population of the licensed indication.

Pasireotide is designated by the EMA Committee for Orphan Medicinal Products as an orphan medicine for the treatment of acromegaly[23]. The prevalence of acromegaly is reported by the company to be around 60 per million, equivalent to 185 patients in Wales[1]. Of these, the company estimates from a range of sources and assumptions that 41 patients would be potentially eligible for treatment with pasireotide. However, prevalence estimates vary widely.

Pasireotide is also licensed and has orphan designation for the treatment of patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. The company estimates a prevalence of 40 per million, equivalent to 123 patients in Wales, of which 4 would potentially meet the licensed indication[1]. Depending on the estimates adopted, pasireotide may or may not meet the threshold for consideration as an ultra-orphan medicine.

Should the New Medicines Group (NMG)/AWMSG consider pasireotide as an ultra-orphan medicine, additional criteria for appraising the medicines will be considered (see Table 7).

Table 7. Evidence considered by NMG/AWMSG.

NMG/AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	Acromegaly is a chronic condition associated with changes in physical appearance, cardiovascular and other forms of morbidity, and premature mortality in those who do not respond to current surgical and medical treatment.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	Pasireotide is licensed for acromegaly patients for whom surgery and/or SSA treatment has not provided adequate control of GH and IGF-1. Pegvisomant is licensed for 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-I concentrations or was not tolerated, but is not recommended for use by AWMSG.
Whether the medicine can reverse or cure, rather than stabilise the condition	Short-term trials with pasireotide have demonstrated achievement of biochemical control and tumour volume reduction only.
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	Pasireotide is a SSA that is reported to have affinity for more somatostatin receptors than first-generation SSAs. Efficacy in patients with inadequate control to the first-generation SSAs has been demonstrated.
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/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	The company notes a report for the Pituitary Foundation exploring the impact of pituitary conditions (including but not specifically acromegaly) on identity and related psychosocial impacts. Based on questionnaires, patients with pituitary conditions report visible and non-visible changes that impact on identity, personality and relationships. Results of the WHOQoL quality of life questionnaire are reported to show dissatisfaction with ability to work and the quality of relationships[28].
Added value to the patient's family (e.g. impact on a carer or family life)	
AWMSG: All Wales Medicines Steering Group; GH: growth hormone; IGF-1: insulin-like growth factor-1; SSA: Somatostatin analogue	

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