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The clinical effectiveness and cost-effectiveness of pegvisomant for the treatment of acromegaly: a systematic review

Martin Connock, Yaser Adi, Sue Bayliss, David Moore

Department of Public Health and Epidemiology
West Midlands Health Technology Assessment Group

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The clinical effectiveness and cost-effectiveness of pegvisomant for the treatment of acromegaly: a systematic review

A WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION REPORT

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Authors:		
	Martin Connock	Systematic reviewer
	Yaser Adi	Systematic reviewer
	Sue Bayliss	Information specialist
	David Moore	Senior research analyst

Correspondence to: Dr Martin Connock
Department of Public Health and Epidemiology
The University of Birmingham

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WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

CONTRIBUTIONS OF AUTHORS:

Yaser Adi developed the protocol, applied inclusion criteria, extracted data on effectiveness and helped design the search strategies. Sue Bayliss designed and implemented the search strategies read and commented on the report. Martin Connock applied inclusion criteria, extracted data, synthesised effectiveness evidence, modified and implemented the economic model and drafted the report. David Moore supervised the project, helped develop the protocol, read and commented on the report.

CONFLICTS OF INTEREST:

No conflicts of interest to declare.

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West Midlands Regional Evaluation Panel

Recommendation

Borderline – apparent level 1 evidence (RCT); in current circumstances not cost-effective.

Anticipated expiry date:

October 2010

GLOSSARY/ABBREVIATIONS AND ACRONYMS

Abbreviation/ Acronym	Definition
CJPG	Cambridgeshire Joint Prescribing Group
CVD	Cardiovascular disease
DopA	Dopamine agonist
GH	Growth hormone
GHR	Growth hormone receptor
GHRH	Growth hormone releasing hormone
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
IGF-1	Insulin-like growth factor 1
IGFBP	Insulin like growth factor 1 binding protein
LASSA	Long acting somatostatin analogue
MM	Manufacturer's model
OGTT	Oral glucose tolerance test
PEG	Pegvisomant
QoL	Quality of life
Rx	Radiotherapy
SC	Standard care
SPC	Summary of product characteristics
SS	Somatostatin
SSA	Somatostatin agonist
WMP	Welsh Medicines Partnership
WMTA	West Midlands Technology Assessment

EXECUTIVE SUMMARY

Background

Acromegaly is a rare disease defined by over-secretion of growth hormone (GH) that in turn induces abnormal over-secretion of a further hormone — insulin-like growth factor I (IGF-1). Together these hormones have multiple and varied metabolic roles and their hypersecretion results in increased tissue growth. In almost all patients acromegaly is caused by a benign tumour in the pituitary gland Acromegaly is associated with a reduced life expectancy, cardiovascular problems and a variety of insidiously progressing detrimental symptoms and clinical changes including enlargement of hands and feet and other organs, coarsening of facial features, fatigue, joint pain and metabolic malfunctions. Early onset leads to gigantism.

Treatments for acromegaly include surgery radiotherapy and pharmacotherapy. Drug options include dopamine agonists and somatostatin analogues. Pegvisomant therapy is licensed as a third or fourth line option when other treatments have failed to normalise IGF-1 levels. Pegvisomant is a genetically engineered GH analogue; it binds to growth hormone receptors, displaces GH and blocks its action. It is administered daily by subcutaneous injection.

Objective

This review assessed the evidence about the clinical effectiveness and cost effectiveness of pegvisomant for the treatment of acromegaly in patients whose IGF-1 levels fail to normalise in response to other treatments.

Methods

The evidence about effectiveness and cost effectiveness of pegvisomant was systematically reviewed. Bibliographic databases were searched from 1980 to March 2007 with no language restrictions. Effectiveness data was extracted from published studies and used for a narrative synthesis of evidence. A deterministic decision analytical model was identified and modified to assess the cost effectiveness of pegvisomant. Sensitivity analyses were performed to investigate the robustness of the cost-effectiveness estimates.

Results

Clinical effectiveness reveiw

Eighteen publications were included. These described one RCT (pegvisomant vs. placebo) and 17 non-randomised or subgroup studies mostly of before and after design. Very little evidence extended beyond one year follow-up.

Main findings:

Pegvisomant rapidly normalised IGF-1 in the majority of patients and substantially reduced IGF-1 in all compliant patients. Reduced IGF-1 was accompanied on average by a doubling in GH levels. Tumour size, at least in the short term, was apparently unaffected by pegvisomant treatment but intermittent monitoring by MRI is widely recommended in view of raised GH levels and the short-term nature of evidence. The drug had a generally safe adverse event profile but in a few patients treatment induced raised liver enzymes that required treatment withdrawal; in a few patients withdrawal needed to be permanent. Treatment was associated with improvement in some of the signs and symptoms of the disease. Limited evidence about disease-risk markers from small, non-randomised, short-term studies indicated that pegvisomant treatment may reduce risk of cardiovascular disease, of diabetes and of maladjusted bone turnover.

Cost effectiveness review

One technology assessment was identified that reported the manufacturer's decision analytical model. This was a simple decision tree design run deterministically that considered a cohort of male patients diagnosed at an age of 45 years and treated for 20 years. The estimated incremental cost-effectiveness ratios (ICERs) were £105,119 / QALY and £194,349 / life year gained, both estimated over a 20 year time horizon from an NHS perspective.

WMTA economic evaluation

We adapted the existing model as necessary so as to reach an economic evaluation relevant to the West Midlands. The ICER over a 20- year time horizon was then estimated at £198,621 / QALY and £578,004 / LYG. Sensitivity analyses using plausible variations in model inputs failed to reduce the ICER below £119,000 / QALY. To achieve an ICER of £30,000 / QALY a substantial reduction in the price of

pegvisomant would be required from £100 per 20 mg vial to £33 / 20 mg vial. Sensitivity analysis using a perfect drug scenario in which all model parameters were selected so as to strongly favour pegvisomant delivered an ICER of £85,235 / QALY and £282,286 / LYG.

Conclusion

Pegvisomant treatment for acromegaly is highly effective for improving patients' IGF-1 level. Evidence is lacking about the long term effects of treatment in respect of improved signs and symptoms of disease, quality of life, patient compliance and safety. An economic evaluation using a simple decision tree model indicated that pegvisomant was very unlikely to represent good value for money according to currently applied standards.

The prevalence of acromegaly (~58 / 10^6) falls just outside the definition for an ultra-orphan disease (< 20 / 10^6) but within the orphan criterion; as such pegvisomant might be considered by some wholly or partially exempt from usually applied value-for-money criteria and subject to other criteria as yet ill defined or incompletely applied by national or local reimbursement bodies.

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AIM OF THE REVIEW

This assessment aims

- To systematically review the evidence on the clinical effectiveness and cost effectiveness of Somavert® (pegvisomant) in the treatment of acromegaly in patients intolerant or incompletely responsive to alternative therapies.
- To model the cost effectiveness of pegvisomant in the treatment of acromegaly in patients intolerant or incompletely responsive to alternative therapies.

The review arose from the request of a consultant in public health medicine within the West Midlands NHS region for information on the clinical effectiveness and cost effectiveness of the growth hormone receptor antagonist Somavert® (pegvisomant) in the treatment of acromegaly. The consultant's interest stemmed from a request by a local endocrinologist for funding for the use of pegvisomant. Searches found no systematic reviews but did indicate that a number of trials had been undertaken.

1. BACKGROUND

1.1 Description of underlying health problem

Acromegaly is a rare endocrine disorder resulting from excessive secretion of growth hormone (GH) (Figure 1).[1] The underlying cause in more than 90% of patients is a benign adenoma of the GH-secreting cells (somatotrophs) of the anterior pituitary. Infrequently (about 20%) these adenomas secrete prolactin in addition to GH. Very rarely acromegaly is due to over secretion of growth hormone releasing hormone (GHRH) by the hypothalamus or to extra-pituitary tumours that secrete GH or GHRH.

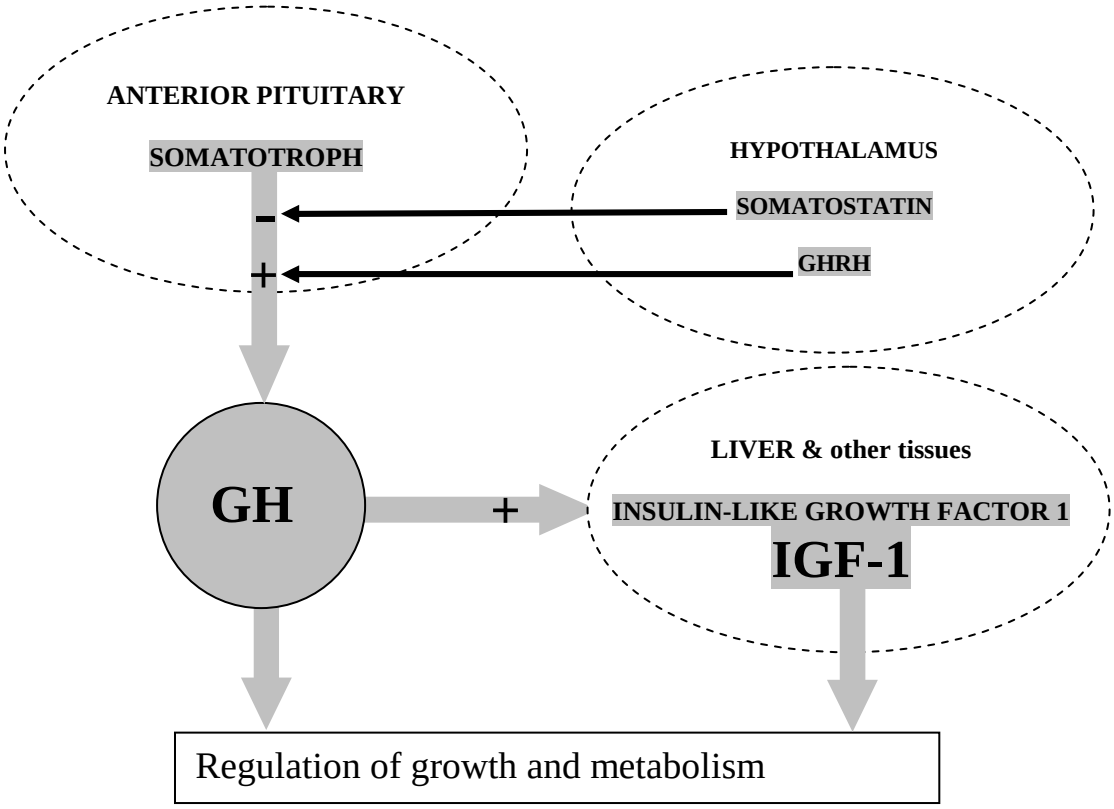

Figure 1 Diagrammatic representation of the role of growth hormone

GH is secreted by pituitary somatotroph cells. Somatotroph population and GH production and secretion are mainly controlled by binding of the hypothalamic hormones GHRH and somatostatin to appropriate receptors on the surface of somatotrophs (Figure 1). GH acts via the GH-receptor (GHR) located mainly in liver and cartilage but also many other tissues. The GHR is a trans-membrane

constitutive dimer with two binding sites for separate ligand sites on the GH molecule.[2] Binding of GH results in signal transduction. GH binding to the GHR promotes synthesis and secretion of insulin-like growth factor 1 (IGF-1) through which many of the actions of GH are mediated. The relative importance of the direct influence of GH and that of IGF-1 secreted in response to GH binding on target tissues is uncertain. Tissue specific knockout of the liver GH-receptor gene does not alter growth in the mouse and implies that circulating IGF-1 (which is primarily derived from the liver) may have little importance compared to paracrine or autocrine derived IGF-1.

The prolonged exposure to elevated endogenous levels of GH and of IGF-1 that occurs in acromegaly results in excessive somatic growth and metabolic dysfunction leading to both direct and indirect tissue damage and secondary systemic illness and reduced life expectancy.

Table 1 Clinical features exhibited in patients with acromegaly (Based on Melmed 2006[1])

SYSTEM	CLINICAL FEATURE
Local tumor	Pituitary enlargement. Visual-field defects. Cranial-nerve palsy. Headache
Somatic	Enlargement including thickness of soft tissue in hands and feet. Gigantism. Prognathism. Jaw malocclusion. Arthralgias and arthritis. Carpel tunnel syndrome. Proximal myopathy. Hypertrophy of frontal bones.
Skin and GI	Hyperhidrosis. Oily texture. Skin tags. Colon polyps.
Cardiovascular	Left ventricular hypertrophy. Septal hypertrophy. Cardiomyopathy. Hypertension. Congestive heart failure.
Pulmonary	Sleep disturbances. Sleep apnoea. Narcolepsy.
Visceromegaly	Enlargement of:- tongue; thyroid gland; salivary glands; liver; spleen; kidney; prostate.
Endocrine / metabolic systems	
Reproductive	*Menstrual abnormalities. Galactorrhea. Reduced libido.*
Endocrine / neoplasia	*Hyperparathyroidism. Pancreatic islet-cell tumors.*
Carbohydrate	*Impaired glucose tolerance. Insulin resistance and hyperinsulinemia. Diabetes.*
Lipid	*Hypertriglyceridemia.*
Mineral	*Hypercalciuria. Urinary hydroxyproline.*
Electrolyte	*Low renin levels. Increased aldosterone levels.*
Thyroid	*Low thyroxine-binding-globulin levels. Goitre*

Clinical features in acromegaly include disproportionate growth, the insidious development of a characteristic physical appearance involving coarsening of facial features and enlarged hands and feet. If onset of disease is earlier than the fusion of long bone epiphyses gigantism results. Patients exhibit varying severities of a spectrum of potentially debilitating clinical features (listed in Table 1) leading to increased morbidity and mortality relative to age and gender matched members of

the general population. An extended discussion of the systemic complications of acromegaly is provided in Colao et al 2004.[3]

Diagnosis

Insidious symptom development and the variety of symptoms for which patients initially seek medical advice results in delayed diagnosis. Delay from onset to diagnosis averaged about 8 years according to a 1999 review[4] in which it was surmised delay would decrease in future due to increasing disease-awareness amongst physicians. Diagnosis is most often eventually made after referral to an endocrinologist. Delayed diagnosis is undesirable as it may allow development of damage that is irreversible by treatment.

Biochemical diagnosis is made by immunoassay of GH and of IGF-1 in blood. The measurement of GH levels is considerably complicated by the pulsatile nature of GH secretion from the anterior pituitary and differences depending on age and sex of the individual. Normal GH levels fluctuate so that about six sharp peaks in concentration occur in each 24 hour period, with much larger peaks during sleep and extremely low levels existing between peaks. Because of the larger somatotroph cell mass GH-secretion troughs may be relatively attenuated in acromegaly.

Consensus guideline criteria[5] for biochemical diagnosis state that if a random sample measure of GH level is < 0.4 μg/litre and IGF-1 is within normal reference range for age and gender then acromegaly is ruled out. If either parameter is in doubt then measurement of the nadir GH following an oral glucose tolerance test (OGTT), with a 75 g load of glucose, is required with GH and glucose being measured every 30 minutes over two hours. A GH nadir of < 1 μg / litre then rules out acromegaly. False positives are possible in patients with concurrent disease states. According to Melmed 2006 the between peak nadir concentrations have been below precise detection limits of older immunoassay methods so that measures from the older generation of diagnostic assays are likely to be less reliable than measures made with modern, more sensitive procedures.[1] Melmed comments[1] that the GH level detected is assay dependent and that further difficulties arise from the lack in uniformity between reference standards and wide inter-assay variation so

that with some commercial kits a nadir of < 1 μg / litre rules out acromegaly but with ultra-sensitive assays this level fails to diagnose about 25% of patients and with these assays a nadir of less than 0.3 μg / litre may be more suitable. In comparing two immuno-assay kits Markkanen et al 2006[6] found one method on average produced GH results 1.4 fold raised above the other, and over the diagnostically critical range around 1 μg / litre the results of one were double those of the other. The guideline-recommended post OGTT nadir value of 1 μg / litre has also been criticised by Pokrajac-Simeunovi and Trainer[7] who conclude that a nadir in the range 0.25 to 0.4 μg / litre represents a better recommendation.

When biochemical diagnosis is positive magnetic resonance imaging (MRI) or computed tomography (CT) scanning is used to locate position and size of the adenoma so that treatment decisions (e.g. with regard to surgery or radiotherapy) can be made. Scanning will therefore confirm biochemical diagnosis. MRI allows detection of an adenoma down to 2 mm diameter.

Epidemiology

The epidemiology of acromegaly was recently reviewed by Holdaway and Rajasoorya (1999)[4] who quoted an annual incidence of 3.3 / million population and a prevalence of 58 / million. A UK study recorded an incidence of “close to three cases per million” and a prevalence of diagnosed cases of “up to forty cases per million”.[8] No gender, racial or socio-economical predispositions have been identified. Therefore the West Midlands Region with a population of approximately 5.5 million might be expected to identify about 16 new cases annually and to have about 300 cases currently registered. The West Midlands Acromegaly Registry lists 430 live acromegaly patients. An average UK health authority, with a population of half a million people would have about 20-30 cases. Only about 10% of GPs would currently be likely to care for a patient with acromegaly and only 30% of GPs will encounter a new case in their career. According to Holdaway and Rajasoorya (1999) the mean age at presentation is 44 years.[4]

The mortality rate in patients with acromegaly is widely quoted to be 1 to 3 times higher than that of an age and sex matched population, and life expectancy is

reduced by about 10 years.[1] Melmed 2006 quotes a standardised mortality ratio (SMR) of 1.48.[1] Stewart recently tabulated published standardised mortality rates dividing studies into two groups: the "*early years*" and the "*last decade*" (Table 2). Meta-analysis (Figure 2) of the latter using a random effects model yields an SMR of 1.42 (95% CI 1.23 to 1.60).

Table 2 Publications reporting mortality rates in patients with acromegaly

PUBLICATION§	NUMBER OF PATIENTS	NUMBER OF DEATHS	STANDARDISED MORTALITY RATIO		
			POINT ESTIMATE	LOWER 95% CONFIDENCE INTERVAL	UPPER 95% CONFIDENCE INTERVAL
Wright 1970[9]	194	55	1.8	1.32	2.28
Alexander 1980[8]	164	45	3.3	2.34	4.26
Nabarro 1987[10]	256	47	1.3	0.93	1.67
Bengtsson 1988[11]	166	62	3.2	2.40	4.00
Rajasoorya 1994[12]	151	32	3	1.96	4.04
Extabe 1993	74	10	3.2	1.22	5.18
Bates 1993 (1995)[13]	79	28	2.63	1.66	3.60
Orme 1998[14]	1362	366	1.6	*1.44*	*1.76*
Swearingen 1998[15]	149	12	1.16	*0.66*	*2.00*
Abosch 1998[16]	214	29	1.277	*0.812*	*1.742*
Shimatsu 1998[17]	979	84	2.1	*1.65*	*2.55*
Beauregard 2003[18]	91	18	2.14	*1.5*	*3.13*
Arita 2003[19]	154	11	1.17	*0.54*	*2.38*
Biermasz 2004[20]	164	28	1.33	*0.87*	*1.87*
Holdaway 2004[21]	208	72	1.22	*0.93*	*1.51*
Ayuk 2004[22]	419	95	1.26	1.03	1.54
K'-Makelin 2005[23]	334	56	1.16	*0.85*	*1.54*
Trep 2005[24]	94	13	1.34	*0.71*	*2.29*

§ list based on that of Stewart 2007 (unpublished) with permission

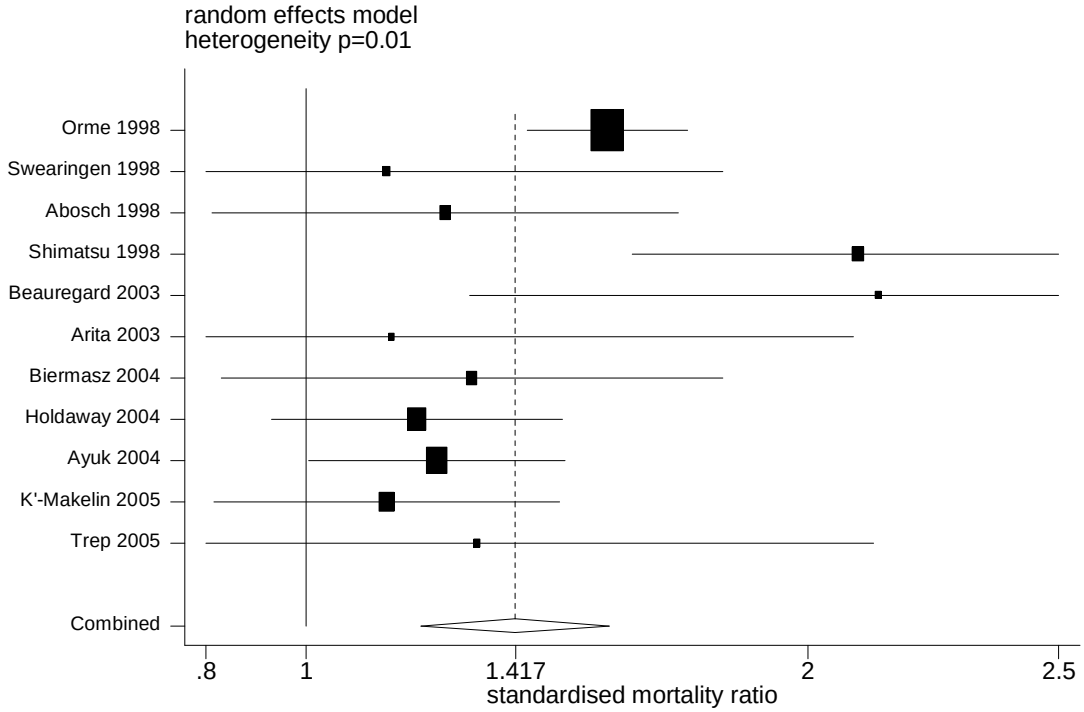

Figure 2 Meta-analysis of last decade published SMRs for acromegaly

The increased mortality rates have been attributed to cardiovascular, cerebrovascular, respiratory and malignant disease.[1,3] The presence of diabetes, sleep apnoea, or hypertension may influence the mortality rate.[1,3]

1.2 Current service provision

The excess secretion of GH in acromegaly is targeted by two treatment strategies, reduction of GH secretion and blocking of GH action. For reducing GH secretion three main treatment options are currently available: surgery, radiotherapy (Rx), and medical treatment with dopamine agonists (DopAs) or somatostatin agonists (SSAs). Effectiveness of current therapies has been reviewed recently by Freda 2003 and by Burt and Ho 2003,[25,26] and consensus and guideline statements about management of acromegaly published.[27-29]

The main aims of treatment include control over tumour growth and over the secretion of GH and of IGF-1, relief from central compressive effects of the tumour, preservation of pituitary function (i.e. the avoidance of hypopituitarism), reversal and prevention of signs and symptoms of disease, improvement in quality of life and prevention of premature death.[1] The main criteria that have been used for

evaluation of therapies has largely depended on the proportion of patients who normalise their blood levels of GH and or IGF-1. Operational application of these criteria has changed with the spread in the availability of improved assay procedures for these hormones.[30]

Surgery

Surgery is the primary treatment for most patients in order to resect or debulk the tumour. Some patients may refuse surgery or may be unsuited to it if the adenoma is judged unresectable and does not endanger nearby vital structures. Either transnasal or transsphenoid surgery are performed for pituitary adenomas.[31] Surgery fails to bring GH and or IGF-1 within normal range in a substantial proportion of patients; success rate across studies ranging from 44% to 74% according to Freda,[25] and further therapy is required. Surgery for acromegaly is more likely successful if performed by a dedicated pituitary surgeon[32,33] and if patients have microadenoma and lower initial GH levels rather than macroadenoma or high initial GH levels.[1] Surgical complications such as vision loss, diabetes, and hypopituitarism can arise, the latter occurring at a rate of 10-20% and up to 30% in one series of patients.[34] Other potential side effects of surgery include leakage of cerebrospinal fluid and meningitis. Some patients require repeated surgery. Surgery may be accompanied with pre-operative medical therapy with SSAs with aim of tumour shrinkage pre-surgery.

Radiotherapy

According to Colao radiotherapy is not a primary treatment option but represents an alternative management tool to be considered for an aggressive adenoma or when patients are unresponsive or intolerant to medical therapy.[27] Conventional radiotherapy invariably induces eventual hypopituitarism while normalisation of GH secretion, if achieved, is delayed by years. Radiotherapy aided by stereotactic devices is recommended and beneficial effects are then faster, within about 5 years, than with conventional radiotherapy; the method may be useful for remnant destruction post-surgery. Increased cerebrovascular mortality and second tumours have been associated with conventional radiotherapy. A large retrospective study of acromegaly patients in the UK National Acromegaly Register[35] concluded that

conventional radiotherapy was an effective and safe means of reducing both serum GH and IGF-1 levels; the proportion of patients with new pituitary hormone deficiencies was 15% to 27% depending on hormone concerned.

Somatostatin agonists (SSAs)

SSAs bind somatostatin receptors on the surface of somatotrophs and inhibit secretion of GH and growth of somatotrophs. Short-term acting and long-acting formulations of SSA therapies have been developed.[36] SSAs vary in their affinity for somatostatin receptor subtypes, and have very prolonged biological half-lives compared to somatostatin (which has a ½ -life of only a few minutes). Examples of SSAs include octreotide and lanreotide. Both are available in long acting (slow releasing) formulations requiring far less frequent administration than the earlier forms of these drugs. Sandostatin Lar® and Somatuline LA® are licensed to be administered once a month and once every 7-14 days respectively.[37] Two slow-release forms of lanreotide are available one administered by deep sub-cutaneously injection the other given intramuscularly; long-acting octreotide is given by intra-muscular injection.

Long-acting SSAs normalise GH levels in about 66% of patients.[36] A further substantial percentage of patients benefit in terms of reduced GH and IGF-1 levels, but fail to have levels completely normalised. Approximately 10% of patients are fully resistant to SSAs. Some tumour shrinkage occurs in many patients treated with SSAs. An increase in tumour size attributable to SSA treatment is rare and induced hypopituitarism is not a significant risk of SSA therapy. Initial, but transient, gastro-intestinal disturbances are common, as are asymptomatic gallstones in the first two years of therapy. No head to head data on relative efficacies and safety of SSAs is available.

Dopamine agonists (DoPAs)

DopAs bind to somatotroph D2 receptors and promote GH secretion in healthy individuals, but paradoxically in some patients with acromegaly who respond to this treatment they inhibit GH secretion. Hence DopAs are a therapeutic option for acromegaly. First introduced in the 1970s today they offer the possibility of low cost relative to other medical therapy options. Dopamine is a brain neurotransmitter with

manifold physiological effects and therefore DopAs cannot be expected to have effects targeted only at problems encountered in acromegaly. Side effects associated with DopAs include nausea, vomiting, postural hypotension, constipation, arrhythmia and CNS effects. Bromocriptine, the first DopA used, is relatively unspecific in binding properties and adverse events are common. DopAs that more specifically bind to dopamine type 2 receptors, such as quinagolide and cabergoline, are available; the latter is taken orally. According to a consensus statement there is no consensus on whether every patient with acromegaly should be given a trial of DopA therapy.[28] Muller and van der Lely concluded "*this class of drugs cannot be considered as medical treatment of choice simply because only a minority of patients."* (those with mixed prolactin GH secretion) "*achieve normal circulating GH and IGF-1 levels*".[36] Colao state "*some patients...particularly those bearing mixed GH/PRL-secreting tumours benefit from first-line treatment with DopAs (cabergoline as drug of choice)*".[27]

Costs associated with pharmacotherapy

DopAs are substantially cheaper than SSAs. In 2002 Moore et al estimated the cost for the first year of treatment with somatostatin analogues to be ~ £12,000 for Sandostatin Lar® (octreotide) and £9,000 for Somatuline LA® (lanreotide).[38] Average annual costs estimated in 2006 by Cambridgeshire Joint Prescribing Group (CJPG) were put at: octreotide £2,000 to £13,000, lanreotide £7,000 to £14,000.[39] Estimated first year costs for dopamine agonists were approximately 10 times cheaper at, according to Moore et al £800 (estimated range £500 - £1,100) for bromocriptine and £1000 (£600 - £2,100) for cabergoline.[38] Average annual cost estimated by CJPG in 2006 were ~£500 and £375 for bromocriptine and cabergoline respectively. It is evident from these values that within class costs are similar. The estimated costs for the second year of treatment were similar to those of the first year for each treatment. A cost effectiveness study based on the above estimates comparing SSAs vs cabergoline concluded that the incremental cost effectiveness ratio was in the region £64.5M (range 29M-300M) per life year saved and £530K (range 253K-3.2M) per QALY gained. These estimates were based on data from observational studies, or on subjective assumptions.

1.3 Description of new intervention

1.3.1 Patients and criteria for treatment with pegvisomant

The excess secretion of GH in acromegaly is targeted by two treatment strategies, reduction of GH secretion and blocking of GH action. Pegvisomant is unique as the only representative of the latter approach. By blocking GH action in the liver pegvisomant brings about a reduction in circulating IGF-1 levels, but GH levels are unlikely to reduce.

According to the Summary of Product Characteristics (Pfizer Febuary 2005[40]) Somavert® (pegvisomant) is indicated for the "*treatment of 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 IGF-1 concentrations or was not tolerated."* These patients may also have elevated GH levels.

A consensus statement published 2000[5] required a patient with "controlled acromegaly" to exhibit a nadir GH concentration of < 1μg / litre (after OGTT), an IGF-1 concentration in the normal range for age- and gender-matched healthy individuals and no clinical activity of acromegaly. The lack of information about normal ranges for IGF-1 and difficulties in assay of GH contribute to uncertainty in the application of these criteria. Pegvisomant is unlikely to fulfil this definition of disease control since it is unlikely to bring elevated GH to < 1μg / litre. The success of Pegvisomant treatment is consequently mainly judged on circulating IGF-1 levels and clinical activity of the disease. Experience with other treatments leads to the assumption that normalisation of circulating IGF-1 level with pegvisomant treatment will be linked to a control over disease progression and possible reversal of some detrimental changes accrued prior to treatment.

It is possible that reduced circulating IGF-1, resulting principally from blocking of hepatic GH-receptors, is indeed a good indicator for potentially more important similar reductions at the local tissue level where pegvisomant also needs to out-compete GH for GH receptors.

The clinical deficits in acromegaly might be mediated directly by excess GH or indirectly via IGF-1 secreted from GH-sensitive target cells, or possibly by a combination of both direct and indirect actions of GH (dual effector theory[41]). Therapies directed at reducing GH secretion, if successful, will be likely to lower both GH and IGF-1 levels whereas pegvisomant, which is aimed at blocking GH action on GH-sensitive cells, reduces IGF-1 but may increase GH. Pegvisomant would need to target GH receptors in all compartments for effectiveness against clinical complications attributable to direct mechanisms; otherwise the raised GH levels induced by treatment might exacerbate rather than alleviate some complications.

1.3.2 Intervention

Somavert®, pegvisomant, is a genetically engineered analogue of GH. The polypeptide is pegylated to reduce immunogenicity and to slow its clearance (biological half-life > 100 hours) and thence increase its availability to bind the GHR. In pegvisomant the amino acid sequence of human GH has been modified at both the sites that bind to the GHR. At one site the modification has resulted in enhanced affinity for the GHR and at the other a complete loss of affinity. The consequence of these changes is that pegvisomant is a GH-antagonist that can compete with endogenous GH for GHRs while failing to activate the receptor because activation requires simultaneous occupation of both binding sites on the GHR molecule. Because the effectiveness of pegvisomant depends on competition with GH the dose of pegvisomant required for treatment will be influenced by GH levels of individual patients which in turn will be influenced by the size, activity and type of adenoma.

Pegvisomant is marketed as a powder in vials containing 10, 15, or 20 mg of pegvisomant and excipients (glycine, mannitol, sodium phosphate buffer salts), together with bottled solvent (distilled water). Powder is reconstituted in 1 ml of solvent and used immediately by subcutaneous injection.

Treatment is initiated by a physician injecting a patient with a loading dose of 80 mg. Thereafter pegvisomant is self-administered by subcutaneous injection starting at 10 mg / day but modified according to monitoring results for circulating IGF-1 levels. Injections are repeated daily. The dose varies according to what is required to bring the individual's IGF-1 to within normal ranges.

Treatment with pegvisomant is potentially life-long. Future therapies might displace it and poor patient compliance might curtail its use. Assuming an average dose of 20 mg/day and taking the cost of a 20 mg vial to be £100.00 (BNF 53[42]) then current annual drug-cost of treatment would be £36,500 per patient. Some additional costs of treatment would derive from monitoring tumour size and blood levels of IGF-1 and of liver enzymes. If a dose of 40 mg / day (highest dose permitted in most trials of

pegvisomant) then drug-cost alone would amount annually to £73,000 / patient. Pegvisomant is approximately 15% cheaper in the US than in UK.

1.3.3 Diffusion

Available evidence indicates that diffusion of Somavert® within the NHS has been minimal. In 2006 both Welsh[43] and Scottish NHS[44] did not support the use of the drug in its licensed indication, the Scottish Medicines Consortium commenting in their advice that " ...*this is an orphan drug but the economic case has not been demonstrated* ". Also in 2006 at least one English region (Cambridgeshire Joint Prescribing Group[39]) made a similar recommendation stating " *the drug should not be prescribed and is not funded for prescribing in Primary or Secondary care.*" . According to expert opinion only about three patients are currently likely to be being treated with Somavert® in the West Midlands region.

2. CLINICAL EFFECTIVENESS

2.1 Methods for reviewing effectiveness

The review was conducted according to a predefined protocol (available on request). The following amendments to the protocol were implemented during the review process: [a] the search strategy was developed and first used in 2005; it was subsequently slightly modified and used again in 2007; [b] studies were only included if they reported data on at least ten patients treated with pegvisomant; [c] initially conference abstracts were to be used for data extraction, subsequently because of their scattered distribution, comprehensive coverage was judged too labour intensive to be practical, and those recovered were used to detect the possible existence of relevant studies missed in other searches.

Search strategy

Initial scoping searches were undertaken to establish if there were any systematic reviews and estimate the nature and volume of primary studies.

Searches of the following bibliographic databases and other sources were undertaken to identify relevant studies:

- Bibliographic databases: Cochrane Library (Wiley) 2007 Issue 1 (CDSR, CENTRAL, DARE), MEDLINE (Ovid) 1950 – 2007 March week 3 , MEDLINE (Ovid) In-Process 3 April 2007, EMBASE (Ovid) 1980 – 2007 week 13 , CINAHL (EBSCO) 1982 – 2007 April 4
- Sources of information on ongoing and unpublished research (including the National Research Register and ClinicalTrials.gov).
- Sources of Abstracts and Proceedings (ZETOC, ENDO 2006 Endocrine Society's 88th annual meeting) as at 4 April 2007
- Citations of relevant studies
- Experts in the field were contacted to check that no published or unpublished studies had been missed.
- Studies listed in systematic and other reviews.

No language or date restrictions were applied. Full details are in Appendix 1.

Inclusion and exclusion criteria

The criteria for including studies for review were:

- Study design: RCTs, quasi-randomised clinical trials, comparative non-randomised studies, or case series if at least 10 patients were included.
- Population: Patients diagnosed with acromegaly.
- Intervention: Treatment with pegvisomant.
- Comparator(s): any other or no treatment, or before and after comparison.
- Outcomes: Any clinically relevant outcomes, changes in IGF-1 levels and GH levels.

Individual case reports, editorials, reviews, and trials on animals were excluded. Studies of Pegvisomant limited only to healthy subjects were excluded. Conference and symposium abstracts were noted and used to check for studies published as full papers. Studies that were multiply published were checked and the most appropriate trial data extracted.

Data extraction strategy and synthesis of evidence

Clinical outcome data and measures of IGF-1 and GH levels were extracted by one reviewer and checked by a second. Disagreements were resolved by consensus

Study heterogeneity precluded meta-analysis and so extracted data was used for a narrative synthesis of available evidence.

Quality assessment strategy

Quality assessment of included studies was performed according to recommendations in the Centre for Reviews and Dissemination handbook 2'nd edition.[45] Quality was assessed by a single reviewer and checked by a second.

RCTs were assessed by examining methods of randomisation, concealment of allocation, blinding, losses to follow up, and methods of analysis (ITT).

For non-randomised studies the following quality issues were felt to be important: study design, patient characteristics, possible sources of bias in patient selection, treatment, outcome measurement. Reports of studies were assessed according to the following questions:

Were eligibility criteria explicit?
Was sample source/selection described?
Were patients assembled at same time?
Was a method of diagnosis stated?
Were clinical details described?
Was individual patient data reported?
Was outcome assessment blinded?
Was blinding method adequately described?
Was follow up time stated?
Were withdrawals stated?
Were reasons for withdrawals stated?

2.2 Results

2.2.1 Quantity and characteristics of research available

Number and type of studies identified

The search of electronic databases yielded 319 citations (see Figure 3), of which 78 were duplicates. Of the remaining 244 citations 212 could be excluded on the basis of the title and or abstract as irrelevant or not fulfilling inclusion criteria. The possible existence of studies not retrieved electronically, was tested by scrutiny of bibliographies of included studies and of lists of conference abstracts and conference poster sessions. These searches failed to yield any further studies. The full text was obtained for 32 citations for further assessment. Figure 3 shows the steps for selection of studies. Of the full texts obtained 14 publications were excluded (see Appendix 2 for reasons for exclusion). Eighteen publications were included for the assessment of effectiveness of which one described an RCT and seventeen described investigations with non-randomised study designs.

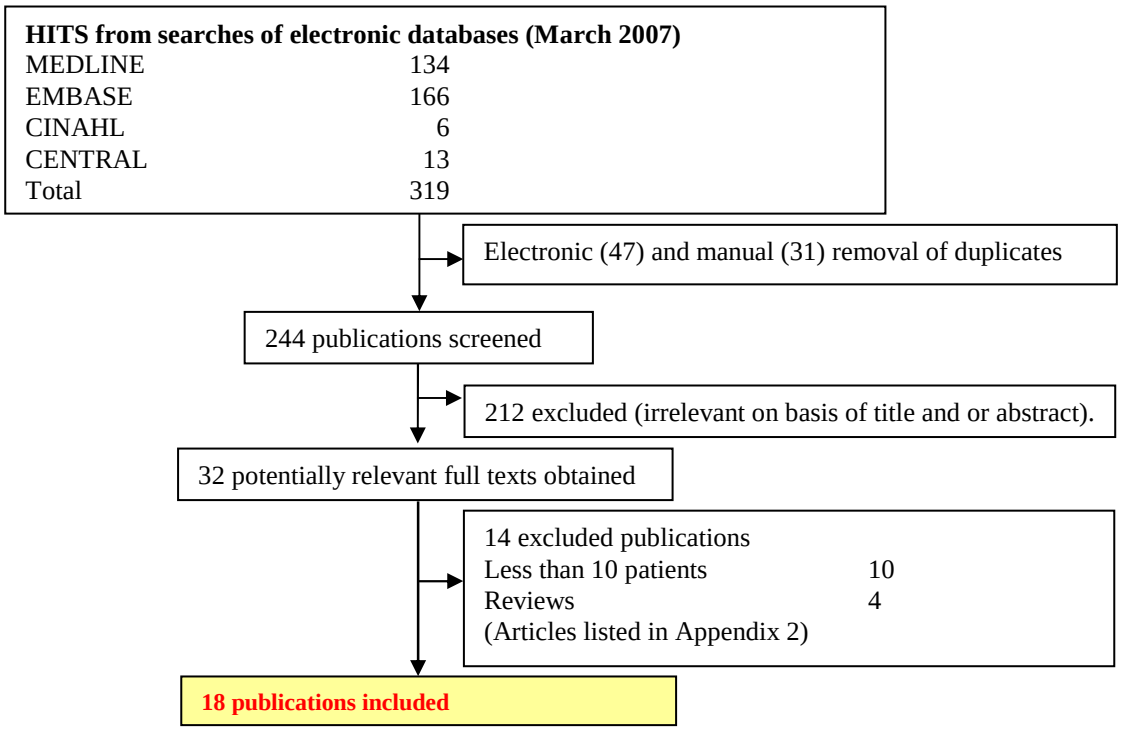

Figure 3 Flow chart showing identification of effectiveness studies

Characteristics of included studies

The main characteristics of the included publications are summarised in Table 3 and further details are provided in Appendix 3.

Study designs employed

Only one randomised trial was found (Trainer 2000); this recruited 112 patients randomised to placebo or three different doses of pegvisomant for 12 weeks.[46] Two other publications described placebo controlled studies (Sesmilo 2002, and Fairfield 2002. [47,48]). The patients in each of these were single centre participants from the Trainer RCT. Outcomes additional to those in Trainer were reported. Because in Trainer randomisation was stratified by IGF-1 level but not by study centre these studies risked numerical imbalance between study arms; they were essentially subgroup studies in which the subgroups were defined by study centre rather than according to patient characrteristics. Sesmilo 2002 also had an uncontrolled extension of pegvisomant treatment beyond 12 weeks and a cross-sectional comparison with matched healthy subjects.[47]

One publication described a retrospective case series (n=142) aimed at monitoring safety of pegvisomant treatment (Biering 2006[49]).

The remaining fourteen publications described before vs. after pegvisomant treatment comparisons, one of which was conducted retrospectively.[50] Three of these publications (Paisley 2006;[51] Parkinson 2004 and Parkinson 2003 [52,53]) included a comparison with matched healthy subjects in a cross sectional (i.e single-time measure) design. In several instances the recruited populations largely overlapped those in another study. Van der Lely 2001[55] reported results for an open label extension of the RCT of Trainer but recruited additional patients and employed a different dose regimen.

Recruited population

Pegvisomant is licensed for use in acromegaly patients who experience suboptimal response to other treatments or who are intolerant of medical treatment required for normalisation (for age and gender) of their GH and IGF-1 levels. One study, Colao

2006,[54] did recruit only patients that had not responded satisfactorily to other treatments and commented with respect to other studies: *"..... all these studies were not designed to investigate the response to pegvisomant in patients with proven resistance to long-term, high dose therapy with somatostatin analogues; these are the patients allowed to receive pegvisomant treatment in Europe according to the product label."*

The only study of robust design (RCT conducted by Trainer 2000[46]) excluded patients who had received long acting SSA therapy in the previous 12 weeks and recruited patients (n=112) only if IGF-1 was at least 1.3 times the upper normal range for age and sex at a second screening prior to recruitment. This second screening was done after cessation of SSAs for at least two weeks and DopAs for at least five weeks. Therefore the status of patients as "*sub-optimal in response to other treatments*" is not clear or guaranteed. However this is not surprising since the study was conducted prior to licensing.

The population recruited by Trainer[46] has been the source of participants for several further published studies. The recruited patients often represented a convenience sample. In this category several types of study may be distinguished:

- Study addressed outcomes, mainly additional to those in Trainer, in a sub-population of those recruited by Trainer that was defined by study centre rather than by patient characteristics.
- Study addressed some or all of the outcomes of the Trainer RCT, sometimes supplemented with additional outcomes, assessed within all or a subgroup of the RCT population supplemented by additional patient recruitment (using consistent inclusion criteria), with follow up extended beyond the 12 weeks of Trainer.

Dose of Pegvisomant and duration of treatment

In most studies a large loading dose (40 to 80 mg) of pegvisomant was administered on day one. In the RCT fixed doses of 10, 15 or 20 mg / day were then given for 12 weeks. In most of the non-randomised studies after the loading dose 10 mg/day was administered but adjusted at timed intervals (e.g. at 6 or 8 week intervals) until

serum IGF-1 levels had declined to normal range for the age and sex of the patient or a maximum dose (e.g. 30 or 40 mg/day) was reached. The dose regimen was halted, suspended or reduced if serum liver enzymes rose to levels giving clinical concern.

Follow up of patients was short term in most studies. Duration of study treatment period varied from as little as 12 weeks in many studies to 12 months in a few, or in the more extended studies to a maximum of 18 months or 2 years for a few patients (see Table 3) .[47,55-58]

Several studies employed dose regimens distinctly different from those in the other studies.[56,59,60] In one study (Jehle 2005,[56] n=10), after achieving IGF-1 normalisation, the interval between dosing was first doubled (to one dose every other day) and then, if IGF-1 normalisation was retained, doubled again. If, after frequency change, IGF-1 reverted to abnormal levels then dose frequency was altered to the previously successful frequency. The Jorgensen 2005 trial (n=11) investigated pegvisomant combined with long-acting SSA.[60] In Feenstra 2005 pegvisomant was administered weekly rather than daily but was adjunct to monthly administration of long-acting SSA treatment, and pegvisomant dose was increased until IGF-1 normalisation was achieved.[59]

Outcomes reported

Serum IGF-1 levels were almost universally reported. GH level was less often reported, probably reflecting the difficulty in measurement because of interference from pegvisomant present in samples. Several studies focussed on risk factors for cardiovascular disease,[51,54,57,61,62] and / or for diabetes.[56,57,60,63] Two studies focussed on markers of bone metabolism.[48,53] Signs and symptoms of disease were monitored in several studies using patient questionnaires with consistent scoring systems and patient blinding to treatment in the RCT.[46,54,56,58] Side effects and blood levels of liver transaminases were commonly, but not universally, measured. None of the studies reported quality of life outcomes.

Table 3 Main characteristics of included publications

STUDY *(Country / region)* Study Design	**POPULATION N** *age (yr [SD]) male (%)* disease duration [SD]Φ	**PREVIOUS TREAMENTS (%)**	**PEGVISOMANT TREATMENT mg/day ΦΦ** **COMPARISON**	**TREATMENT DURATION** ***(follow up)***	**MAIN OUTCOME MEASURES**		**FUNDING**
Trainer 2000[46] *(Europe, US)* Randomised placebo controlled trial	**112*** *48 [14]* *56%* 8 [8] yrs	Surgery 83% Rx*c* 51% Rx*gk* 6% SSA 72% DopA 49% None 3%	Placebo (n=32) or 80 on day 1, then / day 10 (n=26) 15 (n=26) 20 (n=28) PEG vs PLACEBO	12 wks *(12 wks)*	**Serum GH** **Serum IGF-1** **Signs & symptoms** **Tumor volume** **Finger ring size** **Adverse events**	(change from base line). (change from base line; % pnts normal). Free, IGF-1, IGFBP-3 and ALS. (score [0-8] & change from base line) (NMR) (58 standard sizes) (% pnts with headache, pain, nausia, diarrhoea *etc*)	Industry
Van der Lely 2001[55] § *(Europe, US)* Uncontrolled before-after study.	**160** *46 [14]* *59%* 8 [8] yrs	Surgery 84% Rx 59% SSA 73% DopA 48% None NR	Start at 10 & titrate until normalization of serum IGF-1 or maximum dose 40.‡ BEFORE vs AFTER TREATMENT	Mean 425 days *(maximum 18 months)*	**Serum GH** **Serum IGF-1** **Tumor volume** **Adverse events** **Laboratory tests**	(µg/ml: base line (n=152), 6 (n=131), 12 (n=90) &18 (n=39) months). (µg/ml; % pnts normal: base line (n=152), 6 (n=131), 12 (n=90) & 18 (n=39) months). (NMR; change from baseline) (% pnts with headache, pain, nausia, diarrhoea; abs to PEG; *etc*) Serum levels liver enzymes *etc:*;)	Industry
Sesmilo 2002[47] ** § *(Europe, US)* Placebo controlled, subgroup ‡‡ Uncontrolled before-after. & X sectional vs healthy	**48** *45 [2]* *52%* 4.6 [8.2] yrs	Not reported.	10 (n=12), 15 (n=10) 20 (n=12) or placebo (n=14) for 12 wks. Then titrated to normalization of serum IGF-1 or dose of 35 mg/day (n=48). PEG vs PLACEBO BEFORE vs AFTER (X sectional v healthy)	18 months maximum *(18 months maximum)*	**Serum GH** **Serum IGF-1** **CVD markers** **Inflammatory markers**	20 mg PEG (n=12) vs placebo (n=13) change from baseline at 12 wks. 20 mg PEG (n=12) vs placebo (n=13) change from baseline at 12 wks total chol; HDL-chol; LDL-chol; Total chol / HDL-chol; TG; Lipo *a;* homocysteine; glucose; insulin (change base line to end follow up n=34) C-reactive protein (change base line to end follow up n=34)	Industry
Fairfield 2002[48] § *(Europe, US)* Placebo controlled, subgroup ‡‡.	**27** *45.2 [2.3]* *44%* Not reported	Not reported.	Placebo (n=7) or 10 (n=7) 15 (n=6) 20 (n=7) PEG vs PLACEBO	12 wks (*12 wks)*	**Bone markers**	serum osteocalcin, serum carboxy terminal propeptide of procollagen type 1, serum cross-linked*N*-telopeptides of type 1 collagen.	Industry

STUDY *(Country / region)* Study Design	**POPULATION N** *age (yr [SD]) male (%)* disease duration [SD]$^{\Phi}$	**PREVIOUS TREAMENTS (%)**	**PEGVISOMANT TREATMENT mg/day** $^{\Phi\Phi}$ **COMPARISON**	**TREATMENT DURATION** ***(follow up)***	**MAIN OUTCOME MEASURES**		**FUNDING**
Parkinson 2002[62] § *(UK)* Uncontrolled before-after.	**20** *58.7 [ra 28-79] 45%* Not reported	Surgery 70% Rx 60% Medical only 15%	12 wks at various doses then titrated from 10 until IGF-1 normal. BEFORE vs AFTER TREATMENT	Unclear / not reported. *(unclear)*	**Serum IGF-1** **Serum lipoproteins** **Laboratory tests**	(change from base line). total chol; HDL-chol; LDL-chol; apo B; apo A1; TG; Lipo *a;* glucose; insulin; insulin resistance.	Industry
Parkinson 2003a[53]** § *(Europe)* Uncontrolled before-after & X-sectional vs healthy	**16** *52* $^{\theta}$ *56%* Not reported	Surgery 81% Rx 75% Medical only 19%	12 wks at various doses then titrated from 10 until IGF-1 normal, mean dose 20 mg/day. BEFORE vs AFTER TREATMENT & (X sectional v healthy)	Mean 7 months to IGF-1 normalisation *(mean 7 months)*	**Serum IGF-1** **Bone markers**	(change from base line). serum osteocalcin; serum carboxy terminal propeptide of pro - collagen type 1; serum *N* terminal propeptide of procollagen types 1 and 3; serum cross-linked *C*-terminal-telopeptides of type 1 collagen; serum bone alkaline phosphatase; serum vitamin D; serum calcium; serum parathyroid hormone	Industry
Parkinson 2003b[63] § *(UK one centre)* Uncontrolled before-after	**16** *52* $^{\theta}$ *56%* Not reported	Surgery 81% Rx 75% Medical only 19%	12 wks at various doses then titrated from 10 until IGF-1 normal, mean dose 20 mg/day. BEFORE vs AFTER TREATMENT (at 1'st occurrence of IGF-1 normalisation)	Median 9 months to IGF-1 normalisation *(median 9 months)*	**Serum IGF-1** **Serum leptin** **Serum leptin receptor** **Plasma insulin** **Plasma glucose**	(change from base line). median and range Fasting median and range Fasting	Industry
Parkinson 2004[52]§ *(Europe)* Uncontrolled before-after & X-sectional vs healthy	**16** *52* $^{\theta}$ *[ra 27-58] 56%* Not reported	Surgery NR% Rx NR% Just prior PG SSA 31% DopA 50%	12 wks at various doses then titrated from 10 until IGF-1 normal, median dose 15 mg/day. BEFORE vs AFTER TREATMENT (X sectional v healthy)	Mean 7 months to IGF-1 normalisation *(mean 7 months)*	**Serum IGF-1** **Serum IGFBP-1,-2,-3**	(change from base line). median and range	Industry, Danish MRC

STUDY *(Country / region)* Study Design	**POPULATION N** *age (yr [SD]) male (%)* disease duration [SD][Φ]	**PREVIOUS TREAMENTS (%)**	**PEGVISOMANT TREATMENT mg/day [ΦΦ]** **COMPARISON**	**TREATMENT DURATION** ***(follow up)***	**MAIN OUTCOME MEASURES**		**FUNDING**
Barkan 2005[64] § *(Europe, US)* Uncontrolled before-after	**53** *49 [ra 23-81]* *51%* Not reported	PEG 91% SSA.....100% DopA 8% Surgery 83% Rx*c* 60% Rx*gk* 11%	10 start 4wks after last SSA. Titrated at wk 12, 20, 28 according to IGF-1 level. BEFORE vs AFTER TREATMENT	32 wks *(32 wks)*	**Serum IGF-1** **Plasma glucose** **Tumour volume** **Safety**	(change from base line). Fasting glucose; oral glucose tolerance test. NMR Gall bladder ultrasound	Unclear
Jehle 2005[56] *(US)* Uncontrolled before after	**10** *50 [ra 39-67]* *70%* 8.6 [ra 1-24]	Surgery 100% Rx 30% Medical.....80% PEG 20%	40 on day 1, then 10 and then titrated from 10 until IGF-1 normal & frequency adjusted to least for stable IGF-1. BEFORE vs AFTER TREATMENT	12 to 20 months *(12-20 months)*	**Serum IGF-1** **Signs & symptoms** **Tumor volume** **Finger ring size** **Adverse events** **Laboratory tests**	(change from base line). symptom index (0-40), (NMR) (58 standard sizes) (number pnts with headache, insomnia, fatigue, dry skin, *etc*) BMI, blood pressure, glucose, insulin *etc*	NIH US & industry.
Jorgensen 2005[60] *(Denmark)* Uncontrolled before after	**11** *46 [ra 23-71]* *64%* Not reported	Surgery 82% Rx 45% SSA... ..91%	10 for 6 wks then 15 for 6 wks then 15 + SSA for 12 wks BEFORE vs AFTER TREATMENT at timed intervals.	24 wks *(24 wks)*	**Serum IGF-1** **Serum GH & PEG** **Tumor volume** **Laboratory test** **Safety**	total, free & bio-active (change from base line). (NMR) Plasma glucose, Serum insulin Blood levels of liver enzymes	Not reported
Feenstra 2005[59] *(Holland)* Uncontrolled before after	**26[§§]** *51 [13]* *58%* Not reported	Surgery 31% Rx 16% SSA... 100%	Long acting SSA (monthly) + PEG once / wk titrated from 25 mg until normalisation of IGF-1. BEFORE vs AFTER TREATMENT at 42 wks.	42 wks *(42 wks)*	**Serum IGF-1** **PEG** **Safety** **Tumor volume**	(change from base line). weekly dose for IGF-1 normalisation Blood levels of liver enzymes NMR	Not reported
Paisley 2006[51] *(UK)* Uncontrolled before after X-sectional vs healthy	**20** *56 [14]* *55%* Not reported	Surgery 80% Rx 80% SSA....unclear	80 on day 1, then/day 10 increased every 8 wks until IGF-1 normalised. Mean 18. BEFORE vs AFTER TREATMENT & (X sectional v healthy)	Mean 6.5 months (ra 1-16) *(unclear)*	**Serum IGF-1** **CVD markers**	(change from base line). Matrix metallovascular proteinase, endothelial growth factor, Total chol:, TG, glucose.	Industry and EU grant.

STUDY *(Country / region)* Study Design	POPULATION N *age (yr [SD]) male (%)* disease duration [SD]$^{\Phi}$	PREVIOUS TREAMENTS (%)	PEGVISOMANT TREATMENT mg/day$^{\Phi\Phi}$ COMPARISON	TREATMENT DURATION *(follow up)*	MAIN OUTCOME MEASURES		FUNDING
Biering 2006[49] *(Germany)* Retrospective case series	**142** *Not reported* *Not reported* Not reported	Not reported	Not reported OBSERVED vs NORMAL RANGE	Mean 28 wks [SD 20] *(unclear)*	**Safety**	Blood level of liver enzymes (number of pnts at 3 times normal);	Unclear
Colao 2006[54] *(Italy)* Uncontrolled before after	**16** *46*$^{\theta}$ *(ra 28-61)* *47%* Not reported	Surgery 87% Rx 12% SSA... .100% DopA unclear	40 on day 1, then 10 rising by 5 every 6 wks until IGF-1 normalised or 40 reached. BEFORE vs AFTER TREATMENT	12 months *(12 months)*	**Serum GH** **Serum IGF-1** **Signs & symptoms** **Tumor volume** **Finger ring size** **CVD markers** **Safety**	(change from base line). (change from base line; % pnts normal). (score [0-8], change from base line) (NMR) (mm) blood pressure; total chol; Total chol / HDL-chol; TG; fibrinogen; glycosylated hemoglobin; glucose; insulin (change from base) Blood levels of liver enzymes	Industry
Pivonello 2007[57] *(Italy)* Uncontrolled before after	**17**[§§§] *48*$^{\theta}$ *(ra 27-61)* *47%* Not reported but ≥ 6 months	Surgery 82% Rx 12% SSA... . 82% DopA unclear	40 on day 1, then 10 rising by 5 every 6 wks until IGF-1 normalised or 40 reached. BEFORE vs AFTER TREATMENT	6–18 months *(6–18 months)*	**Serum GH** **Serum IGF-1** **Echocardiography** **CVD markers**	(change from base line). (change from base line; % pnts normal). (LV mass, LV mass index; ejection fraction; LV posterior wall thickness; interventricular septum thickness); blood pressure; total chol; Total chol / HDL-chol; TG; fibrinogen; glucose; insulin (change from base); HOMA; BMI.	Industry
Schrieber 2007[58] *(Germany)* Uncontrolled before after	**177**[§§§§] *40.5 [12.7]*$^{\theta\theta}$ *47%* Mean 9.1 yrs	Surgery 90% Rx 43% Medical 94%	Mean 16.5 [SD 7.7] (94% pnts 10 to 30). BEFORE vs AFTER TREATMENT	Maximum 2 yrs *(Maximum 2 yrs)*	**Serum IGF-1** **Signs & symptoms** **Tumour volume**	(change from base line; % pnts normal). (score [0-8], change from base line) (NMR)	Industry
Parkinson 2007[50] *(Europe, US)* Retrospective Uncontrolled before-after.	**118**[§§§§§] *44*$^{\theta}$ *(ra 27-61)* *58%* Mean 9.1 yrs	Rx 58%	80 on day 1, then 10 titrating every 8 wks by 5mg until iGF-1 normalised or	Mean 12 months [SD7] *(12 months SD 7)*	**IGF-1 normalisation**	Influence of baseline IGF-1 & GH levels, previous Rx, sex, age, weight; on dose of PEG required.	Unclear

Φ time since diagnosis. ΦΦ unless otherwise stated. **θ** median. **θθ** age at diagnosis. § Study population wholly or mostly of participants from the RCT of Trainer 2000[46]. §§ only 19 of 26 participants analysed at 42 weeks. §§§ 14 of 17 patients were also participants in Colao 2006[54]. §§§§ Eligible population 229, 52 not evaluable. §§§§§ Eligible population 147, 29 not evaluable. * Patients excluded from the study if treated with a long-acting SSA within 12 weeks before enrolment. ‡ Most patients were those entered into the RCT of Trainer; the description of initial dosing regimen inconsistent. ‡‡ Subgroup of participants from Trainer, subgroup defined by study centre not by patient characteristics. ** In part of this study US patients from Trainer were analysed, stratification by centre may have allowed proper randomisation but this is not clear. In part of this study (cross sectional comparison) patients were compared to matched healthy controls. Unclear if prospective or retrospective (ie post hoc) analysis of available serum samples. ¥ Describes patients with raised transaminase levels that were participants of study by Schreiber[58]. ALS: acid-labile subunit of IGFBP-3. BMI: body mass index. Chol: cholesterol. CVD: cardiovascular disease. DopA: dopamine analogue. HDL: high density lipoprotein. HOMA: homeostatic model adjustment index. IGFBP: IGF binding protein. LDL: low density lipoprotein. Lipo a: lipoprotein little a. LV: left ventricle / left ventricular. NMR: nuclear magnetic resonance scan. PEG: pegvisomant. pnts: patients. Ra: range. Rx: radiotherapy. Rxc: conventional radiotherapy. Rxgk: gamma knife radiotherapy. SSA: somatostatin analogue. TG: triglyceride

2.2.2 Quality of included studies

The quality of the single included RCT (Trainer) was moderate to good. Details of assessment are given below.

Table 4 Quality assessment of the RCT of Trainer2000

QUALITY ITEM		COMMENT
Was assignment of treatment described as random?	YES	
Was method of randomisation described?	NO	
Was the method really random?	CAN'T TELL	Only information is that the "*Randomisation schedule was prepared by a statistician*".
Was allocation of treatment concealed?	CAN'T TELL	No mention of concealment.
Who was blinded to treatment?	DOUBLE BLINDED	No description of who was blinded.
Was method of blinding adequately described?	NO	No description of method.
Were eligibility criteria described?	YES	Unclear if all patients fulfill the licensed indication
Were groups comparable at study entry?	YES	
Were groups treated identically apart from the intervention?	YES	
Was ITT used?	NO	
Were withdrawals stated?	YES	
Were reasons for withdrawals stated	YES	
Was a power calculation done?	CAN'T TELL	May have been done but not reported.

The quality assessment of the other studies is summarised in Appendix 4. Most were of moderate quality. The weakest quality elements were a lack of clear information about the sampling frame from which study participants had been selected and a lack of description of the selection methods employed. The rarity of acromegaly may have dictated the use of convenience samples in most studies but this was not explicitly reported. The before-after study of Colao 2006[54] was of good quality, it provided individual patient's data, described patient selection and accounted for withdrawals.

2.2.3 Clinical Effectiveness Results

2.2.3.1 Symptoms and signs of acromegaly

Randomised controlled trial evidence

The RCT of Trainer 2000,[46] reported on the effectiveness of pegvisomant in alleviating the signs and symptoms of acromegaly. Data was elicited from patients using a questionnaire with a rating scale of 0 (no symptoms) to 8 (severe, incapacitating) for each of five symptom categories: soft tissue swelling, headache, joint pain, excessive sweating, fatigue.

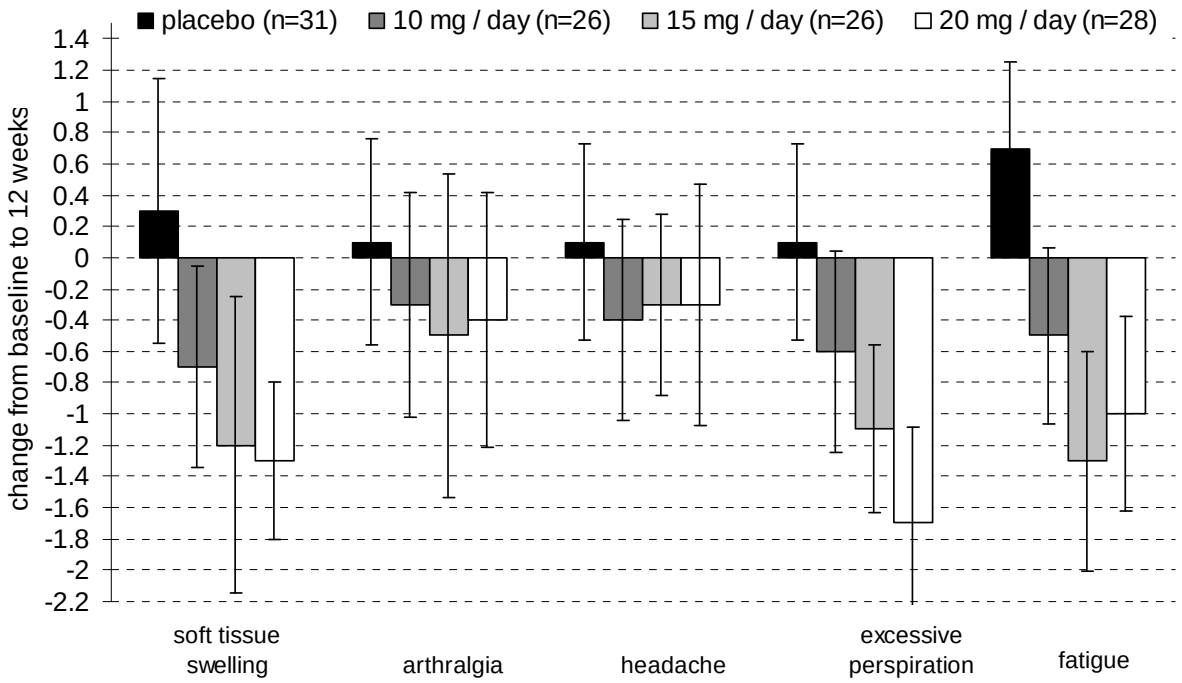

Figure 4 Change in signs and symptoms of acromegaly reported in the RCT of Trainer 2000.

Mean and 95% confidence intervals of change at 12 weeks from baseline.

The observations reported by Trainer are summarised in Figure 4 . Relative to placebo, statistically significant ($p \leq 0.05$) improvements were noted for the two high dose groups with regard to scores for soft tissue swelling and excessive perspiration, and for all treatment groups for fatigue. Change in total score (summing scores from all five symptom categories) showed statistically significant improvement for all treatment groups relative to placebo.

Trainer also reported finger ring-size measures that likely reflect soft tissue swelling. Relative to placebo both 15 mg / day and 20 mg /day groups exhibited statistically significant decrease in ring size measures at 12 weeks of treatment.[46]

Non-randomised evidence

The uncontrolled non-randomised studies of Jehle,[56] Colao[54] and of Schreiber[58] reported data on the effectiveness of pegvisomant for relief of signs and symptoms of acromegaly. The small studies of Calao and Jehle (n=16 and n=10) enrolled only patients whose IGF-1 had not been normalised with SSA treatment, and in the larger study of Schreiber most patients had stopped SSA because of failure to control IGF-1.

Jehle investigated the same symptom categories as Trainer and also employed the 0 to 8 scoring system with mean treatment period of 15.3 months [SD 4.6]).[56] The total score at baseline was 12.3 (95% CI 6.0 to 18.6) and post-treatment was 8.6 (95% CI 3.9 to 13.2) and a trend for improvement was noted.

Colao reported similar results, again with none of the individual symptom categories (soft tissue swelling, headache, joint pain, excessive sweating, fatigue, paresthesia) reaching statistically significant improvement with treatment but results showing a favourable trend.[54] These two studies may be underpowered for this outcome.

Schreiber[58] used an 8 point scoring scale and symptom questionnaire similar to that of Trainer[46] but with two additional categories (general physical condition, and numbness or tingling of limbs (paresthesia); in this study only 62 patients (of a possible 229) completed the questionnaire at baseline and only 56 at 6 months into treatment. Statistically significant improvements (6 months vs. baseline score) were reported for soft tissue swelling, headache, joint pain, general physical condition, and for total score. The reliability of these findings is called in question because of likely sampling bias.

Jehle reported statistically significant reduction after treatment relative to baseline in finger ring-size measures.[56]

2.2.3.2 Tumour volume

Randomised controlled trial evidence

In the RCT of Trainer after 12 weeks of pegvisomant treatment the group mean tumour volumes were very similar to baseline in all groups (Appendix 6) and no individual patient exhibited a clinically significant increase in volume.[46]

Non-randomised evidence

Several studies reported about the effect of pegvisomant treatment on pituitary volume monitored using MRI. Results for small studies are provided in Appendix 6.

In the study of van der Lely (2001) mean change from baseline for 131 patients was not statistically significant (group mean change: – 0.033 ml; 95% CI; – 0.15 to +0.08; p = 0.353 for difference from zero change). Two patients had progressive tumour growth that required treatment, the authors could attribute no cause, and there was no relationship between duration of pegvisomant treatment and change in tumour size.[55]

The large observational study (n = 229) by Schreiber reported on tumour volume results at baseline and after treatment in 102 patients.[58] In 12% of these patients increase in tumour size was observed by treating-physicians at a median time into treatment of 48 weeks. The scans for these patients were re-examined by an experienced neurosurgeon. In five of these twelve this blinded re-analysis failed to verify the initial evaluation (an apparent error rate of 42%). In three of the twelve cases increase in volume was judged to be consistent with progression established prior to start of pegvisomant treatment, and in four of the twelve cases the volume increase was verified as occurring after the start of pegvisomant therapy. In two of the latter this was interpreted as rebound increase after shrinkage that had been induced by SSA therapy prior to its withdrawal. Unfortunately no re-examination was carried out of the scans looked at by treating-physicians who evaluated them as showing no increase in tumour volume (n = 90).

2.2.3.3 Reduction in serum IGF-1 and achievement of normal levels.

Randomised controlled trial evidence

The commonly adopted criterion of successful treatment is the lowering of serum IGF-1 to within normal range (according to age and gender). In the RCT of Trainer IGF-1 normalisation was the primary outcome and this study provides the most robust data with respect to short term treatment (follow up 12 weeks).[46] Details are provided in Appendix 7.

At baseline patient IGF-1 levels were at least 1.3 times above the top of the normal range. Figure 5 summarises IGF-1 levels for placebo, 10 mg, 15mg and 20 mg / day pegvisomant groups at 0, 3, 6, 9, and 12 weeks of treatment. Statistically significant reductions in IGF-1 occurred after treatment in all groups except placebo; at all time intervals after baseline statistically significant differences were observed for all the treatment group means vs. placebo group means.

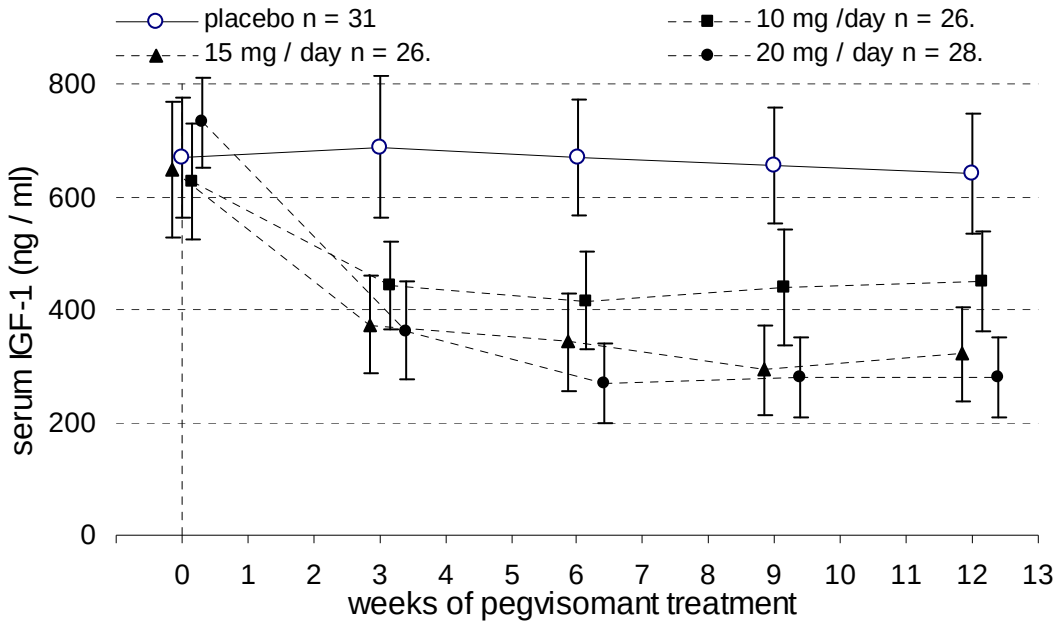

Figure 5 Decline in IGF-1 concentration with 12 weeks pegvisomant treatment (RCT of Trainer 2000).

Redrawn from Trainer. Group mean IGF-1 with 95% confidence intervals. Time points slightly displaced to avoid overlap. Data for 3, 6 and 9 weeks calculated from published graph.

By three weeks of treatment the mean IGF-1 level in all three pegvisomant groups had reduced and was significantly less than in the placebo group where the mean IGF-1 did not change appreciably. Beyond 3 weeks the mean IGF-1 levels in treatment groups fell further, except for the 10 mg / day group. A distinct dose response relationship was evident with 15 and 20 mg / day more effective than 10 mg / day.

At 12 weeks the proportion of patients with normalised IGF-1 levels was 10%, 38%, 75% and 82% in placebo, 10 mg, 15 mg, and 20 mg groups.

Non-randomised evidence

The non-randomised studies of van der Lely 2001,[55] Schreiber 2007,[58] Colao 2006,[54] Feenstra 2005,[59] Jorgensen 2005,[60] and Jehle 2005,[56] also reported IGF-1 levels after pegvisomant treatment. Details are provided in Appendix 7 and the main findings for the large studies (van der Lely and Schreiber) are summarised below.

Van der Lely[55] titrated pegvisomant dose so as to achieve normal range IGF-1 with a maximum allowed dose of 40 mg / day. Figure 6 shows the reported IGF-1 levels.

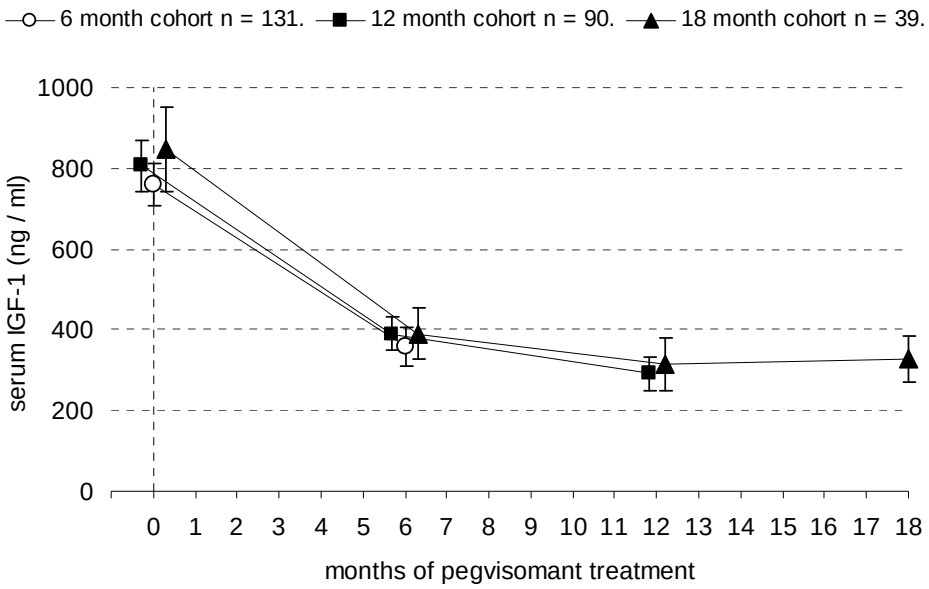

Figure 6 Decline in serum IGF-1 with length of pegvisomant treatment (data of van der Lely 2001)

Redrawn from van der Lely. Group mean IGF-1 with 95% confidence intervals. Time points slightly displaced to avoid overlap. Data for 6, 12 and 18 months calculated from published graph.

At 12 months 97% of patients were reported to have IGF-1 levels within normal range; however it is unlikely this was an ITT analysis.

Out of a total population of 229 Schreiber collected IGF-1 data for 157 patients at baseline and for 147, 102, and 39 patients after 6, 12 and 24 months (Figure 7).[58] Mean group values reported by Schreiber correspond closely those in the study of van der Lely 2001.[55] At baseline 11% had normal range IGF-1 and at 6, 12 and 24 months of treatment 64%, 71%, and 76% were in normal range. These percentages

are distinctly lower than the 97% reported by van der Lely. Schrieber et al comment this may be due to better patient compliance and superior monitoring for dose adjustment in a clinical trial compared to the real world clinical practice reflected in their study.

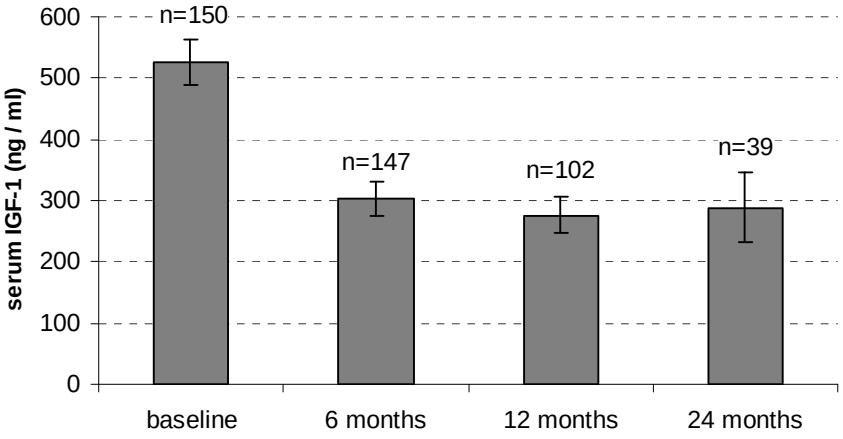

Figure 7 IGF-1 levels (and 95% CI) at various times after start of PEG treatment (Schreiber 2007)

Colao reported individual IGF-1 levels for 16 patients that fitted the licensed indication for pegvisomant.[54] Of 14 patients evaluated eight (57%) reduced IGF-1 to within normal range and three more to within 1 to 1.3 times normal range.

The results reported in several additional small studies were similar to those above; details are provided in Appendix 7.

2.2.3.4 Effect of pegvisomant on GH levels

This outcome was reported in several studies including the 12 week RCT of Trainer and its 18 month open label extension reported by van der Lely.[46,55] Details are given in Appendix 8 and main findings summarised below.

Randomised controlled trial evidence

Pegvisomant treatment substantially increased serum GH levels above baseline levels (of approximately 8 ng / ml). The results are summarised in Figure 8.

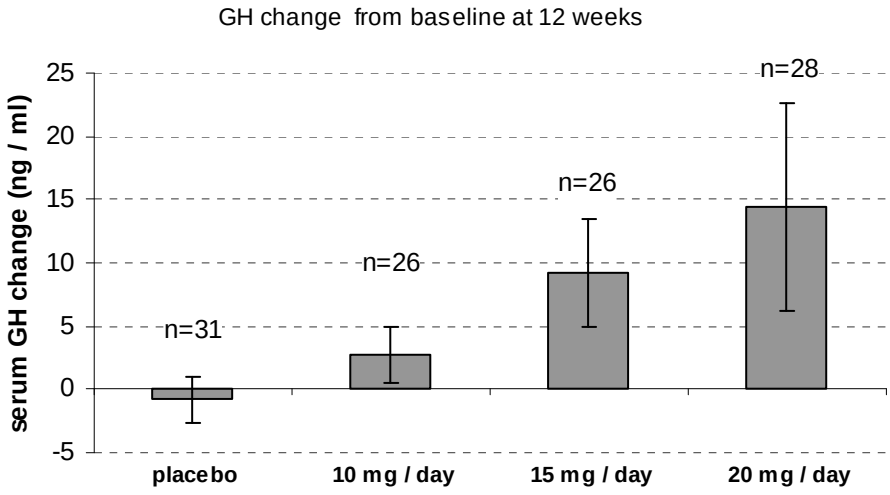

Figure 8 Change in serum GH (ng / ml) from baseline to 12 weeks (Trainer 2000)

For patients receiving placebo the change from baseline was small and not statistically significant. For all treatment groups the increase from baseline reached statistical significance. A dose response relationship was evident and the two higher dose groups exhibited a statistically significant greater increase than the 10 mg / day group.

Non-randomised evidence

The results reported by van der Lely indicate that with pegvisomant treatment beyond 12 weeks group mean GH levels remain at substantially elevated levels relative to baseline.[55] The results are summarised in Figure 9 and compared with those reported by Trainer.

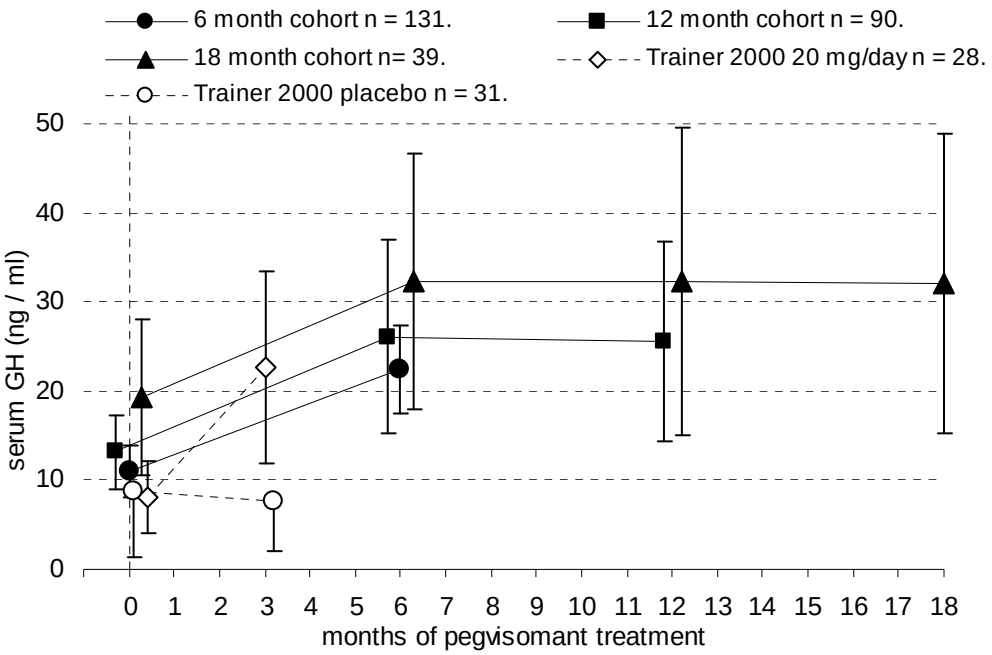

Figure 9 Group mean GH levels and 95% CI reported by Trainer and van der Lely.

Colao reported individual GH levels for 16 patients that fitted the licensed indication for pegvisomant.[54] The mean baseline GH ranged from 3.4 to 74.8 ng / ml (mean 23 ng / ml; 95% CI 10.9 to 35.0). After treatment, discounting one patient who failed to inject pegvisomant, the range was 6.3 to 145 ng / ml (mean 33.1; 95% CI 11.3 to 54.9). Not all patients increased their GH level. The range of change from baseline was –17 to + 52 ng / ml and group mean change from baseline was +10.8 ng / ml (95% CI –1.7 to +23.3).

The results reported in several additional small studies were similar to those above; details are provided in Appendix 8.

2.2.3.5 Adverse events, safety and patient withdrawal from treatment.

In the RCT of Trainer the high dose group (20 mg / day) experienced slightly higher rates of adverse events than the placebo group (12 weeks follow up).[46] The adverse events (Table 5) were not associated with withdrawal from study except for two patients who withdrew from receiving pegvisomant because of persistent headache (n = 1) or due to raised serum level of liver enzyme (n = 1); one placebo patient withdrew for persistent headache also.

Table 5 Rate of adverse events reported in Trainer (2000)

	RCT (Trainer, 2000) ¶			
Adverse event	PLACEBO n = 32	10 mg / day n= 26	15 mg / day n = 26	20 mg / day n = 28
Upper respiratory tract infections	5 (16%)	5 (19%)	4 (15%)	5 (18%)
Headache	4 (12%)	3 (12%)	2 (8%)	3 (11%)
Injection-site reaction	0	2 (8%)	1 (4%)	3 (11%)
Pain	2 (6%)	2 (8%)	1 (4%)	4 (14%)
Diarrhoea	1 (3%)	1 (4%)	0	4 (14%)
Nausea	1 (3%)	0	2 (8%)	4 (14%)
Flatulence	0	0	1 (4%)	3 (11%)

¶ *Number of patients (%) with adverse events that occurred in at least 10% of patients.* ¶¶ *Number of patients (%) with adverse events occurring in > 1% and judged potentially causally related to PEG treatment.* PEG: pegvisomant

The occurrence of a variety of adverse events associated with pegvisomant treatment were reported in the longer follow up studies of van der Lely,[55] Schreiber,[58] and Jehle;[56] these are detailed in Appendix 9.

Van der Lely[55] reported higher rates of adverse events than Trainer. Of 160 participants who received pegvisomant 30 (19%) withdrew from treatment for various reasons (9 for adverse events, 5 for lack of efficacy, 12 “voluntarily”, and 2 each were lost to follow up or “violated protocol”). Withdrawal rates in Schreiber[58] were unclear.

Levels of liver enzymes

Van der Lely reported that during study serum levels of liver enzyme activities remained within normal range.[55] Schreiber reported abnormally raised serum levels of liver enzymes (mainly ALT) in 21 of 229 (9%) patients treated with pegvisomant; in 12 of these the levels were ≥ 3-fold above normal. Of the 12 with very elevated

levels seven patients returned to normal during pegvisomant treatment, levels returned to normal in four patients after withdrawal of pegvisomant and in one patient levels remained high (γ-GT) but pegvisomant continued. Details of six of these patients were reported by Biering 2006.[49] In this report 6 of 142 (4%) withdrew permanently from pegvisomant treatment because of raised liver enzyme levels.

The 12 month study of Colao[54] recruited 16 patients of whom 4 (25%) withdrew or were withdrawn during study: one patient failed to inject pegvisomant, one because of rise in serum transaminase enzyme level, one through inability to follow the protocol and one because of poor compliance.

2.2.3.6 Additional outcomes reported in non-randomised or subgroup studies.

A variety of further outcomes were reported, including some indicative of risk of diabetes (GTT, fasting glucose and insulin), risk of cardiovascular disease (blood lipid profiles, inflammatory markers, echocardiography), and of maladjusted bone turnover (markers for collagen turnover, vitamin D, alkaline phosphatase). Most of these studies involved patients previously recruited into other studies (mainly Trainer and / or van der Lely), and retrospective laboratory analyses of serum samples for surrogate markers of disease-risk. Except for one study[63] information was lacking about conditions and duration of serum sample storage and the number of freeze-thaw cycles before assay of markers. Details from these studies are provided in Appendix 10 and main findings are summarised below.

Four studies reported about the statistical significance of pegvisomant-induced changes from baseline in the levels of several risk markers for cardiovascular disease. [47,51,54,62] The findings were inconsistent between studies and no firm conclusions justifiable (Appendix 10).

Increased prevalence of cardiac problems is thought to lead to increased mortality in acromegaly.[3] Pivonello used Doppler echocardiography to investigate changes induced by 18 months of pegvisomant treatment.[57] Statistically significant changes

indicative of improvement in cardiac structure and function were observed (Appendix 10).

Two studies, Parkinson 2003a[53] and Fairfield 2002,[48] presented data on serum markers of bone metabolism. The results (Appendix 10) support the proposition that pegvisomant reduces bone turnover in acromegaly patients; how this translates to patient benefit requires further investigation.

Several small non-randomised studies reported the effect of pegvisomant on laboratory measures relating to insulin and or glucose metabolism; studies included those of Barkan 2005 (n=53),[64] Parkinson 2002 (n=20),[62] Parkinson 2003b (n=16),[63] Colao 2006 (n=16),[54] Jehle 2005 (n=10),[56] Jorgensen 2005 (n=11).[60] The general direction of findings was for a favourable change indicative of improved metabolic adjustment. The significance of these findings for patient well-being is difficult to judge.

2.2.4 Summary of effectiveness evidence

Quantity and quality of available evidence

- One international multi-centre industry-sponsored placebo controlled RCT (n=112), two studies that described outcomes among single-centre participants from the RCT, and 15 uncontrolled non-randomised studies were included in this report.
- The RCT was of moderate to good quality but of short treatment duration (12 weeks). Except for two studies that reported on more than 100 patients the non-randomised studies were small; most were of relatively short duration, the longest follow up being 24 months for a few patients only.
- Information about the sampling frame for selection of study participants and about patient compliance, was inadequately or rarely reported. It is unlikely that all of the patients in many studies fitted the licensed indication for pegvisomant.
- No study compared pegvisomant with an alternative pharmacotherapy.

Key findings

- At adequate daily dosage subcutaneous pegvisomant considerably reduced serum IGF-1 in patients with acromegaly. Under clinical trial conditions 12 weeks of pegvisomant normalised IGF-1 levels in approximately 90% of patients. Continued treatment maintained IGF-1 at these reduced levels.
- Limited evidence from non-randomised studies indicated that the licensed population (patients who previously failed to normalise their IGF-1 with SSA therapy) may be more difficult to control with pegvisomant than average patients, and that in real world clinical practice success in normalising IGF-1 may be considerably less than 90% because of poor patient compliance (because of the requirement for daily subcutaneous injection) and or imperfect dose adjustment.
- Administration of pegvisomant at doses required to normalise IGF-1 levels induces a large rise in serum GH on average to approximately double pre-treatment levels.

- Pituitary adenoma size was apparently unaffected by pegvisomant treatment in the great majority of patients, at least in the short term. However, available evidence was short term or incomplete; the possibility that pituitary feedback mechanisms contingent on prolonged exposure to pegvisomant-induced elevation in GH levels could have lead to enlargement of tumours requires long term MRI monitoring and vigilance.
- Patient questionnaires indicated that relative to placebo pegvisomant had statistically significant superiority in alleviating some of the signs and symptoms of acromegaly including soft tissue swelling, fatigue, and excessive perspiration. Relative to placebo pegvisomant showed a trend for improvement in joint pain and headache. In a before vs. after study that was susceptible to selection bias pegvisomant induced statistically significant improvement for soft tissue swelling, headache, joint pain and general physical condition but not fatigue, excessive sweating or numbness of limbs.
- There was some evidence from small non-randomised studies that pointed to changes in surrogate markers for disease-risk that indicate pegvisomant may possibly reduced risk of CVD, diabetes and maladjusted bone turnover.
- There was a lack of empirical evidence about the impact of pegvisomant on patient health related quality of life or patient survival, or about patient compliance with a long term daily regimen of pegvisomant administration.

2.2.5 Assessment of effectiveness

Acromegaly is rare and the subpopulation licensed for pegvisomant small, so that difficulties in patient recruitment may partly explain the existence of only a single RCT, and the participation of overlapping populations of patients amongst multiple studies. Most of the non-randomised evidence about effectiveness of pegvisomant comes from studies that, because of difficulties in recruiting, used “convenience” samples of patients; they were susceptible to biases of patient selection and in some cases incomplete follow up. In general, study size was small and follow up was short with little or unclear reporting about withdrawals from treatment.

To estimate the effectiveness of the intervention for the licensed indication it is desirable that the investigated study participants should reflect the licensed population. Unfortunately most studies provided only averaged baseline characteristics for the whole study population without indicating the proportion fitting this “licensed population”. It is not possible to state the proportion of patients in the RCT of Trainer trial fitted the “licensed indication” and it should be noted that this study preceded licensing. Patients who had received long acting SSA within 12 weeks before enrolment were barred from the study. A criterion for recruitment required that IGF-1 should be at least 1.3 times above the top of the normal range at a screening visit before study start. But this screening followed at least 2 weeks after cessation of SSA treatment and five weeks after stopping DopA therapy, so that in these patients IGF-1 was likely to rise substantially prior to baseline measurement; unfortunately the number of patients receiving these medical treatments just prior to enrolment was not reported nor was the proportion of recruited patients whose IGF-1 was in normal range prior to the screening.

Convincing evidence indicated that all patients that receive an adequate dosage of pegvisomant experience significant reductions in circulating IGF-1 levels. A substantial proportion of such patients are brought within normal range IGF-1 for their age and gender. [46,55,59,54,58]

In contrast to IGF-1, the levels of GH appear on average to be considerably increased by pegvisomant treatment. This evidence comes from the twelve week RCT of Trainer[46] and from the uncontrolled extension of this study (van der Lely[55]) and also from two small non-randomised studies.[54,60] The individual patient data provided in the small study of 16 patients by Colao shows GH does not increase in all patients treated with pegvisomant.[54] Increased levels of GH incompletely blocked by pegvisomant could in theory exacerbate clinical deficits of acromegaly. The available evidence about effectiveness of pegvisomant does not support occurrence of such exacerbation (see below), but the totality of evidence is thin and predominantly very short term and therefore this consideration cannot be ruled out.

The reported effects of pegvisomant on signs and symptoms of acromegaly were elicited using patient questionnaires. The twelve week RCT demonstrated a positive trend in favour of pegvisomant for all the signs and symptoms reported.[46] The validity of these results depends on efficient blinding of patients from treatment received. Methods for blinding were not described and tests of blinding success were not performed or not reported. We would expect lack of blinding to influence answers given in questionnaire via patient knowledge about whether placebo or active drug was received, rather than any knowledge about what dose of active drug was received. Therefore, the fact that a clear dose effectiveness relationship was observed in the results for signs and symptoms, reflecting that for laboratory-determined IGF-1 levels, indicates that blinding was probably effective and the results reliable. The data from non-randomised studies lends support to these findings.[54,56,58]

Pituitary adenoma size is apparently unaffected by pegvisomant treatment in the great majority of patients, at least in the short term.[54,55,56,58,59,60,64] However, available evidence is short term or incomplete; the possibility that pituitary feedback mechanisms contingent on prolonged exposure to pegvisomant -induced elevation in GH levels could lead to enlargement of tumours requires long term MRI monitoring and vigilance.

In a small proportion of patients pegvisomant induces raised liver enzyme levels that necessitate temporary, or in a few instances permanent, treatment withdrawal.[49,54,58] However the limited evidence available indicates that pegvisomant has a generally mild adverse event profile. Antibodies to pegvisomant appear rarely to have been measured. Evidence is lacking about any relationship between anti-GH antibodies and decrease in efficacy of pegvisomant or an increase in adverse events frequency. Possible development of antibodies should be monitored.

The introduction of long acting SSAs, which reduced the requirement for daily SSA injection, resulted in improved patient compliance for this form of therapy. Pegvisomant treatment requires subcutaneous self-injection daily and may not be popular with some patients in a real world setting. Unfortunately no good empirical evidence was found about long term rates of patient compliance with pegvisomant therapy.

Increased mortality in acromegaly has been associated with cardiovascular problems. The effect of pegvisomant upon risk indicators for CVD is therefore of interest. However the uncontrolled non-randomised studies included in this review did not provide wholly consistent or easily interpreted information with regard to risk indicators. A single small 18 month non-randomised study provided evidence that pegvisomant induces favourable changes in cardiac structure and performance.[57]

3. ECONOMIC ANALYSIS

3.1 Methods for economic analysis

Search strategy

Search details are provided in Appendix 1. The following bibliographic databases were searched:

- MEDLINE(Ovid) 1950 to March Week 3 2007
- EMBASE (Ovid) 1980 to 2007 Week 13
- Cochrane Library (Wiley) 2007 Issue 1
- NHS EED, OHE HEED to April 2007.

Inclusion criteria

Studies were included if they satisfied the following criteria:

Study design: Cost-effectiveness, cost-utility and cost-benefit studies. Health economic reviews were also included.
Population: People with acromegaly
Intervention Pegvisomant
Comparator Any alternative treatment
Outcomes: Quality of life, costs, or incremental cost-effectiveness ratio.

Inclusion criteria were applied by one reviewer and checked by another. Included studies were reviewed, assessed for quality, and data extracted by one reviewer and checked by another.

Studies that reported health-related quality of life (QoL) results for patients with acromegaly but did not satisfy the inclusion criteria were noted and if judged relevant were used to inform the economic analysis.

Quality assessment and analysis

A single study was included; this described and assessed the quality of a decision analytic model submitted to NHS Wales by the manufacturer of pegvisomant. The NHS Wales quality assessment of the manufacturers model used the criteria suggested by Weinstein 2003.[65] For the purposes of the present report the NHS Wales critique of the manufacturer's model is summarised and supplemented with our own critical comments relating to quality. The economic section of this report then goes on to modify the manufacturer's model so as to generate cost effectiveness estimates of relevance to the West Midlands.

3.2 Results of cost effectiveness review

The search yielded 114 publications. A single publication satisfied inclusion criteria; it described a decision analytic model of pegvisomant treatment for acromegaly versus standard care (SC) that was appropriate to the UK NHS and to the population licensed for use of pegvisomant. This Health Technology Assessment by the Welsh Medicines Partnership (WMP) was completed in 2005 and made available on the internet.[43] The Welsh report contains a critique of an economic model of cost effectiveness that was submitted by the manufacturer (Pfizer Limited), together with the results of a re-run of this model using "preferred parameters" judged by WMP to provide an improved estimate of cost effectiveness. We requested model-access from the manufacturer and were provided with an appropriate working Excel spread sheet. The decision tree structure of the manufacturers model (MM) is shown below.

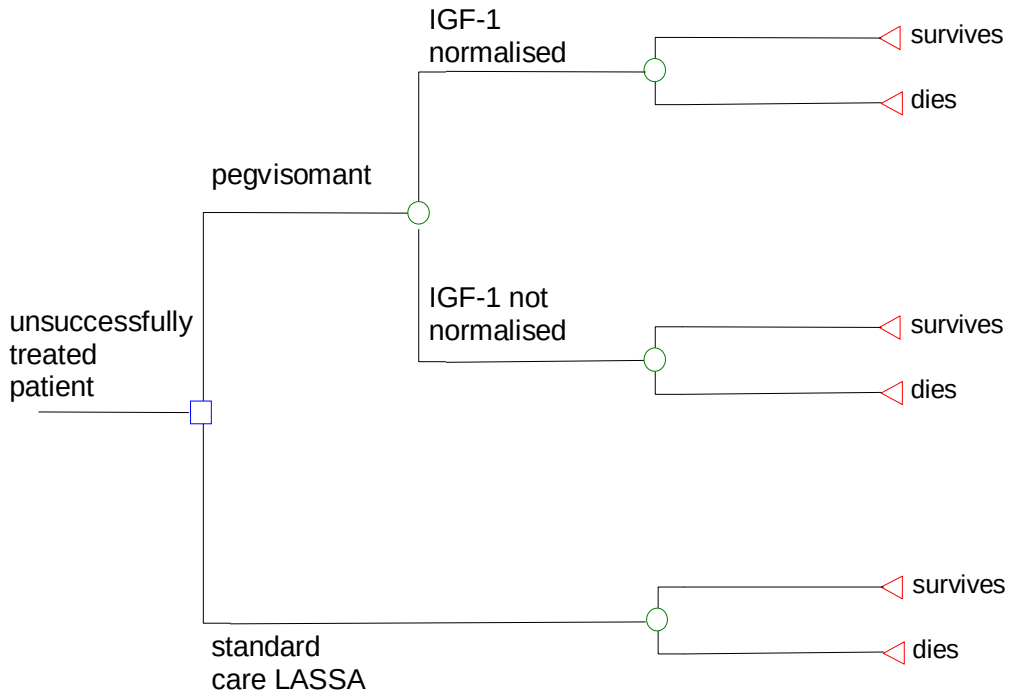

Figure 10 Decision tree structure of the manufacturer's model

The following section describes the essentials of the manufacturer's model (MM) and summarises the main aspects of its critique by the WMP together with the West Midlands Technology Assessment (WMHTA) comments on elements that we consider important.

3.2.1 Manufacturer's model (MM)

The MM compared pegvisomant with long acting SSA treatment (Sandostatin® LAR® or Somatuline Autogel®) for a population that failed to normalise IGF-1 under all treatments save pegvisomant. In the base case, treatment continued for 20 years and the time horizon was 20 years. It considered cohorts of 100,000 male patients diagnosed at average age of 45 years. The benefits of pegvisomant treatment derived from improved survival and improved utility (QoL). The survival of unsuccessfully treated patients (taken as the comparator population) was obtained by applying a SMR to the life table of the general population. To calculate survival benefit it was assumed that 92% of pegvisomant treated patients were responders and attained the survival probability of the general population while 8% were non-responders and remaied with the survival probability of standard care (SC) patients. Thus survival benefit was calculated from the difference between the life table for untreated patients and that for treated patients (Figure 11).

Utility gain was taken to be equal to the disutility of patients experiencing a coronary event (0.83-0.75) and was experienced by the 92% responders; the remaining 8% of pegvisomant-treated patients did not experience utility benefit. The same gain was applied for each year of treatment.

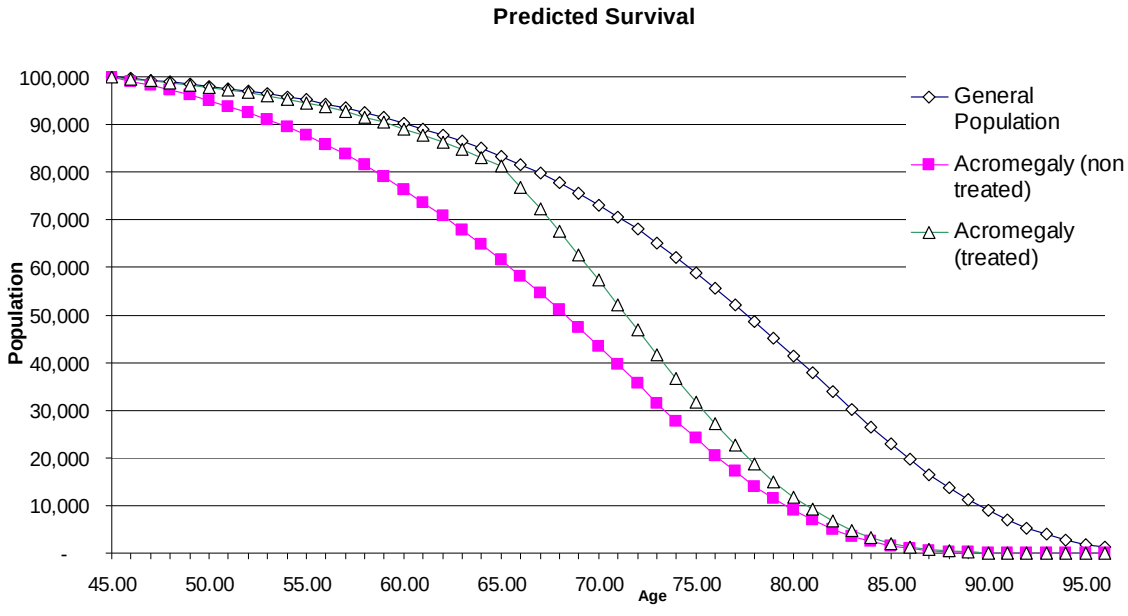

Figure 11 Survival of patients in the manufacturer's economic model

The comparator “unsuccessfully treated” SC patients received LASSA. The incremental cost used in the model was only the difference between acquisition costs of pegvisomant and of LASSA (£27,375 - £13,289 = £14,086 per annum). Both benefits and costs were discounted at 3.5%.

The model generated £ / life years gained (LYG) and £ / quality adjusted life years (QALY) gained over a 20 year time horizon. Univariate sensitivity analysis included other time horizons and a life-long analysis. The results are summarised below (Table 6).

Table 6 ICERs generated by manufacturer’s model with manufacturer’s input parameters

	Time horizon	ICER
QUALITY ADJUSTED LIFE YEARS GAINED	4 Yr:	£160,960 / QALY
	5 Yr:	£157,233 / QALY
	10 Yr:	£138,915 / QALY
	20 Yr:	£105,119 / QALY
	Life-time:	*£84,265 / QALY*
LIFE YEARS GAINED	4 Yr:	£1,375,974 / LYG
	5 Yr:	£1,082,426 / LYG
	10 Yr:	£488,684 / LYG
	20 Yr:	£194,349 / LYG
	Life-time:	*£113,282 / LYG*

3.2.2 WMP critique of manufacturer’s model and WMTA comments

WMP undertook a detailed critique of the MM using the checklist devised by Weinstein et al 2003.[65] Full details of the critique can be found in the WMP publication.[43] Important elements of the WMP critique are listed and commented upon below (direct quotes from WMP are in italics)

1] *The model is structured so that the inputs and outputs are relevant to the AWMSG. The costs reflect the perspective of the NHS in Wales.*

- Comment

  This applies for the West Midlands also.

2] Does the model appropriately capture the full impact and cost of treatments?

Probably not. There is no consideration of costs other than drug acquisition costs (for example, monitoring of liver function tests), and the long-term impact of pegvisomant on survival is based on assumptions as no data are available. No reliable measures of health state utilities were included.

- Comment

  Annual MRI scan monitoring of pituitary adenoma is recommended during pegvisomant therapy; NHS reference costs (Code RBF1) sets this at £244. Other costs relating to comorbidities exist but were not considered. These have been estimated to differ according success of treatment (controlled or uncontrolled disease status).[66]

3] Does the model appropriately represent the patient population(s) of concern?

Data on the survival of the general population do not appear to relate to Welsh population statistics. Utility scores are based on English data of patients with cardiovascular disease, and may not be applicable to Welsh acromegalic patients.

- Comment

  Survival of the general population in the MM was based on English males only whereas the WMP preferred model input was for a mix of Welsh males and females. The difference between these survival curves is shown below (Figure 12). Utility scores based on cardiovascular patients, if inappropriate, would probably be equally so for Welsh and English patients. At the time of the WMP assessment no publications had reported utility scores for acromegaly patients.

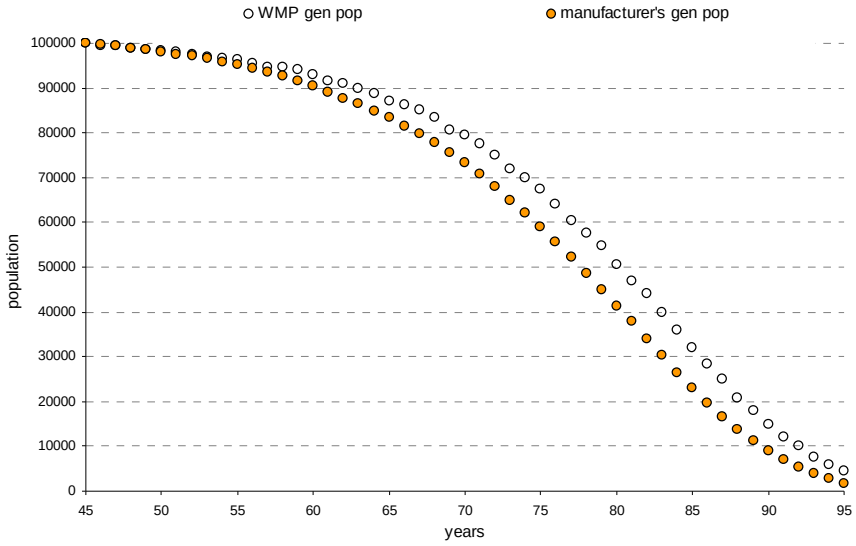

Figure 12 Survival of the general population: manufacturer's model & preferred parameters of WMP.

4] Were appropriate methods used to include patients' treatment and disease history and effects on event rates? *No specific description was given of the hypothetical cohort of patients in terms of what proportion might be unresponsive or intolerant to treatment. Likewise, no description was given of the health states of patients entering the model.*

- Comment

  In generating the survival for pegvisomant treated patients the manufacturer assumed 92% were responsive. The limited effectiveness evidence indicates that all patients that continue pegvisomant do indeed respond strongly in terms of lowered IGF-1 and many normalise; however it is clear from the reviewed effectiveness studies (e.g studies of Schreiber 2007,[58] and Colao 2006,[54]) that the drop out rate is likely to be substantial and this was ignored in the MM.

5] Does the model clearly list and justify structural assumptions, and likely impacts on outcomes? *A simple model was employed, which is appropriate when only limited data are available.*

6] Does the model structure fit with the clinical theory of the disease process? *The model captures the essentials of the disease, in terms of survival and crude quality of life. It does not include health states that may be appropriate to account for the significant complications associated with acromegaly. There is no consideration of cardio-respiratory complications or malignancies, for instance.*

- Comment

  There is a lack of evidence to inform reliably on different health states. The model described three health states: active disease, disease remission (equivalent state to matched member of the general public) and death. A direct link was assumed from IGF-1 levels to quality of life (QoL) and survival.

7] Does the model clearly list and justify structural assumptions, and likely impacts on outcomes? *A simple model was employed, which is appropriate when only limited data are available. However, no structural sensitivity analysis was performed to test the robustness, or otherwise of the model structure.*

8] How were structural aspects tested by the modeller (e.g. clinical opinion, literature review, clinical guidelines)? *It would appear that the design of the model was driven by epidemiological data on survival and clinical trial data on treatment efficacy.*

9] Are time horizons appropriate, given the disease, treatments and decision context (1-year, 10-year, lifetime)? *A 20-year time horizon was presented for the base-case. In addition, estimates of cost-effectiveness adopting a lifetime and other time horizons were given.*

- Comment

  Given diagnosis at 45 years, the chronic nature of the disease condition, the short term clinical evidence (since pegvisomant was only developed recently) and the presumed long term treatment regime both short and long term time horizons would seem appropriate.

10] Is there a full description of a thorough review process identifying data values? *No reviewing process had been conducted; data values were taken from selected studies.*

- Comment

  The present report systematically reviewed effectiveness evidence published up to March 2007.

11] Are the sources of data values fully described and appropriate? *The effectiveness of pegvisomant was determined from one study. It was assumed that the utility deficit associated with acromegaly was the same as that experienced with a coronary event, and that pegvisomant could fully reverse this. There is no supportive evidence to suggest that either of these assumptions is valid. Data on the SMR for acromegaly was from one source, and did not necessarily apply to uncontrolled acromegalic patients. The SMRs were derived from a study of 79 male and female patients, of whom 50 had radiotherapy and /or bromocriptine; 6 had no treatment. This population would certainly differ from the population for which pegvisomant is indicated.*

- Comment

  Since the licensed population are patients resistant to all treatments in terms of normalising their IGF-1 and GH levels then, since the detrimental effects of raised GH (and IGF-1) will not have been opposed, one might expect this population to have a poor survival outcome despite various treatments, and therefore a high SMR compared with other acromegaly sub-populations. It is surprising therefore that the WMP preferred a SMR that was substantially lower than many reported values.

12] Are there clear criteria for data inclusion / exclusion? *No justification was given as to why these studies, and not others, were selected.*

13] Are there appropriately documented value ranges for data parameters for sensitivity analysis? *The ranges of parameter values chosen for the sensitivity analyses – for effectiveness of pegvisomant and SMR multiplier – were selected from the literature. An arbitrary range was chosen for utility drop with acromegaly. Total costs and benefits were presented both in the discounted and undiscounted form.*

- Comment

  Since the WMP assessment several HRQoL studies have been published using a disease specific instrument (acromegaly quality of life questionnaire AcroQoL); one of these also reports utility values for acromegaly patients.

14] Are there full details on data preparation to generate parameter values (e.g. meta-analysis, relative risk rates, estimation of utility, calculation of transition rates)? *Parameter estimates were extracted directly from the literature. There were no details of costs (other than drug acquisition costs) or full justification for the choice of utility drop experienced with acromegaly.*

15] Were survival data appropriately extrapolated / modelled (e.g. Weibull, exponential)? *The life-table method used in the model is appropriate. The issue is*

around whether the intermediate health outcomes observed in short term trials, may be extrapolated to survival benefits over 20 years.

16] Was uncertainty adequately incorporated in the model using appropriate sensitivity structures and analyses? *Multiple univariate sensitivity analyses were conducted on key model parameters, including utility score, effectiveness of pegvisomant, SMR multiplier and discount rates. Costs associated with treating acromegaly were not subjected to sensitivity analysis. No probabilistic sensitivity analysis was conducted.*

3.2.3 WMP modification of MM

The WMP team preferred different input parameters for the model. The changes WMP introduced were based on:

a) A revised SMR estimate derived from a more recent study of 1362 acromegalic patients (366 deaths) in the UK. This study provided a pooled male and female SMR for all cause mortality of 1.55 [95%CI 1.35, 1.76] for the age group 35 to 59 years.
b) Revised life-table probabilities for males and females in Wales.
c) Proportions of males and females based on age-specific Welsh population statistics.

The resulting survival curves are represented below

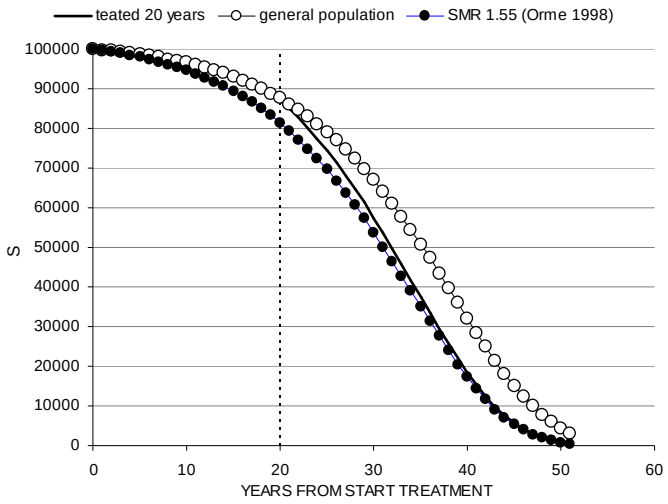

Figure 13 WMP preferred survival curves

Using the revised inputs the discounted cost per life-year gained was £748,480. This greatly exceeds the estimate provided by the manufacturer (base case: £194,349 / LYG). The WMP team considered pegvisomant not to be cost-effective.

3.2.4 WMTA changes to MM

According to the Summary of Product Characteristics (Pfizer Febuary 2005[40]) Somavert® (pegvisomant) is indicated for the "*treatment of 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 IGF-1 concentrations or was not tolerated."*

"Failure to normalise IGF-1" requires some sort of definition of normality which, as discussed in section 1.3.1, presents operational problems. Clearly, whatever the definition of normalisation, a reduction in IGF-1 without normalisation is a possible or likely response to treatments. Under these circumstances, in the absence of pegvisomant, patients may or may not be provided with somatostatin analogue (SSA) treatment. The question then arises as to what is an appropriate comparator against which cost effectiveness of pegvisomant should be judged? The most likely possibility is continued SSA treatment in the proportion of patients partially responsive and tolerant plus care for co-morbidities, and care for co-morbidities without specific acromegaly-directed pharmacotherapy in the proportion intolerant or unresponsive to SSAs. In the MM all patients in the comparator arm received SSA treatment. For the WMTA model we consulted expert clinical advice about the proportion of patients that would receive SSA therapies.

In the MM some patients (8%) continue with pegvisomant for up to 20 years without responding to treatment. This is unlikely to occur in practice. Further, the MM did not allow for withdrawal from pegvisomant treatment. The WMTA modifications changed the model so that non-responders and non-compliant patients ceased pegvisomant treatment and reverted to SC so no longer gaining survival or utility benefit. A decision tree revised model is shown below.

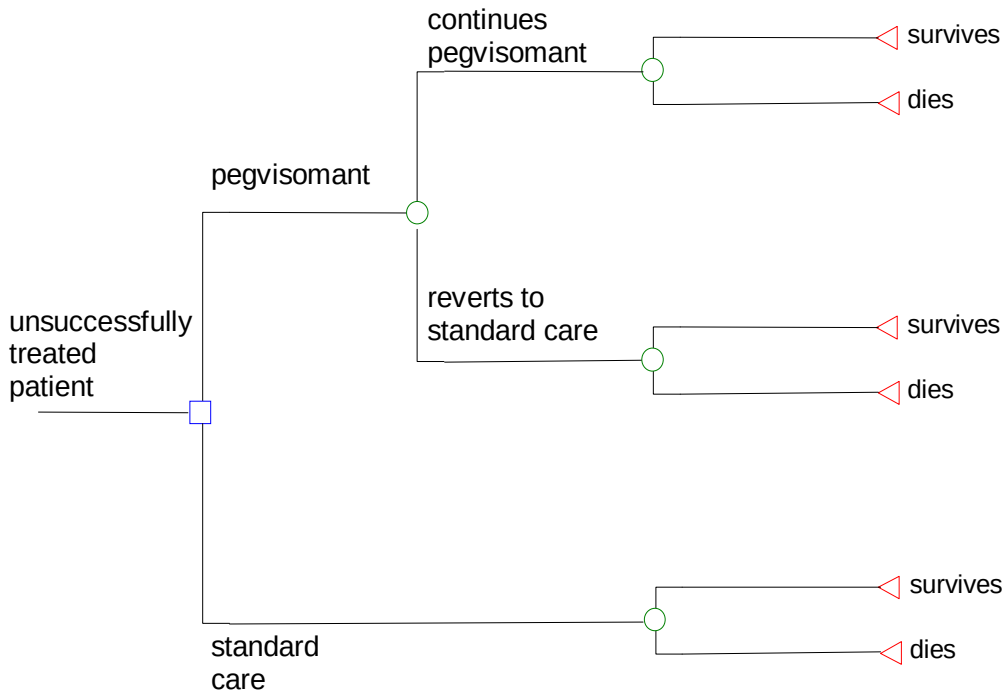

Figure 14 Schematic of the decision tree used by WMTA

For base case WMTA applied a time horizon of 20 years. Sensitivity analysis considered several other time horizons.

Expert clinical advice considered neither the manufacturer's nor WMP model inputs were wholly satisfactory. Therefore inputs were modified. Although the revised inputs improve upon those used previously, all are associated with considerable uncertainty. Therefore three strategies were adopted:

a. For the base case, inputs were selected according to expert clinical advice and taking account of effectiveness evidence published up to March 2007. Compared with previous applications of the model (by the manufacturer and WMP) some changed inputs favour the intervention while others favour the

comparator. All versions assume that for some patients pegvisomant can fully eliminate deficits in QoL and survival.

b. Sensitivity analysis was done around the potentially important drivers of the base case ICER.
c. A “perfect drug” scenario was adopted in which all inputs were set to strongly favour the intervention and the resulting ICER was judged to be a reasonable estimate of the absolute lowest ICER possible with pegvisomant treatment.

WMTA input changes from previous model inputs include survival curve for the general population, SMR for the SC population, utility gain from pegvisomant treatment, treatment options in the comparator population, costs associated with pegvisomant treatment, costs associated with SC treatment. These are listed in more detail below.

3.2.5 WMTA input values for effectiveness parameters

a) Survival for the general population over the age of 45 years.

The MM considered English males only, while a mix of Welsh males and females was used by WMP. WMTA used survival statistics for an equal mix of English males and females age 45 years (Figure 15).

b) Survival for the SC population; choice of SMR.

SMR values chosen by WMP to derive the survival curve for the “comparator” population was quite different to that used by the manufacturer (1.55 compared to 2.63) and this was the main driver of the discrepant results. According to the license the only patients eligible for pegvisomant are those whose disease remains uncontrolled by all alternative treatments; this is a small sub-group of the total acromegaly population. According to expert opinion many will have received radiotherapy; studies indicate this to be an independent indicator of poor survival.[22,23] Recent SMR estimates will mostly reflect survival of successfully treated patients, whereas earlier estimates (e.g. prior to the present decade) more likely reflect survival of unsuccessfully treated or untreated patients. Table 2 lists SMRs reported in early and last-decade studies. Several early studies report SMRs

> 3.0 and one early study (Bates 1993,[13] SMR 2.63) was performed in the West Midlands. Meta-analysis of older studies yielded a pooled SMR of 2.52 [*95% CI: 1.82 to 3.22*] compared to 1.417 [*95% CI: 1.229 to 1.604*] for last-decade studies.

The WMTA base case used an SMR of 2.63 as most appropriate to the West Midlands (Figure 15) and took the UCI of the pooled estimate (SMR of 3.22) as an upper limit for sensitivity analysis, and a 10% higher value (SMR 3.6) than the highest value reported for the perfect drug scenario. The effect of SMRs on survival profile is illustrated in Appendix 11.

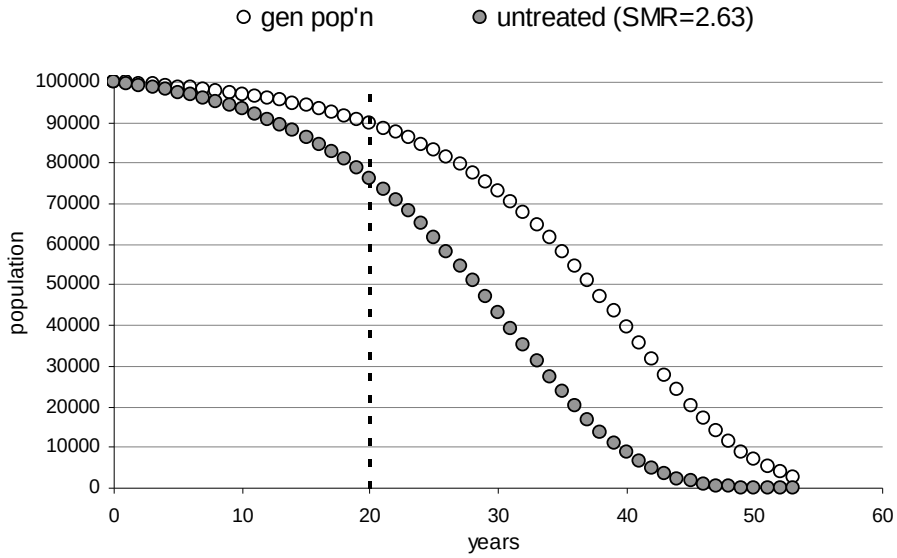

Figure 15 Survival of general population and SC population used for base case.

c) Effectiveness of pegvisomant treatment:— survival. Both manufacturer and WMP assumed that 92% of pegvisomant treated-patients gained survival probability of the general population and that 8% gained no survival benefit (retaining the survival of standard care patients). The 92% success was based on the rate of IGF-1 normalisation reported by van der Lely.[55] This is problematical because there was no guarantee that patients corresponded to the licensed specification and because it was unclear whether patient attrition was taken into account. Although the uncontrolled study of Colao 2006[54] was much smaller and was non-randomised it probably better reflects the licensed population, the likely early rate of patient withdrawal and the % that normalise IGF-1. In this study ~20% of patients were non-compliant early in the first year. IGF-1 was normalised in 75% of compliant patients and all patients experienced very substantial reductions in IGF-1 level; those that did

not normalise closely approached normality. It was assumed that 20% patients drop out in the first year and gain no survival or utility benefit and that compliant patients gain the survival probability and QoL of the general population. If the 80% patients that are compliant remain so then survival profiles are generated as shown in Figure 16 .

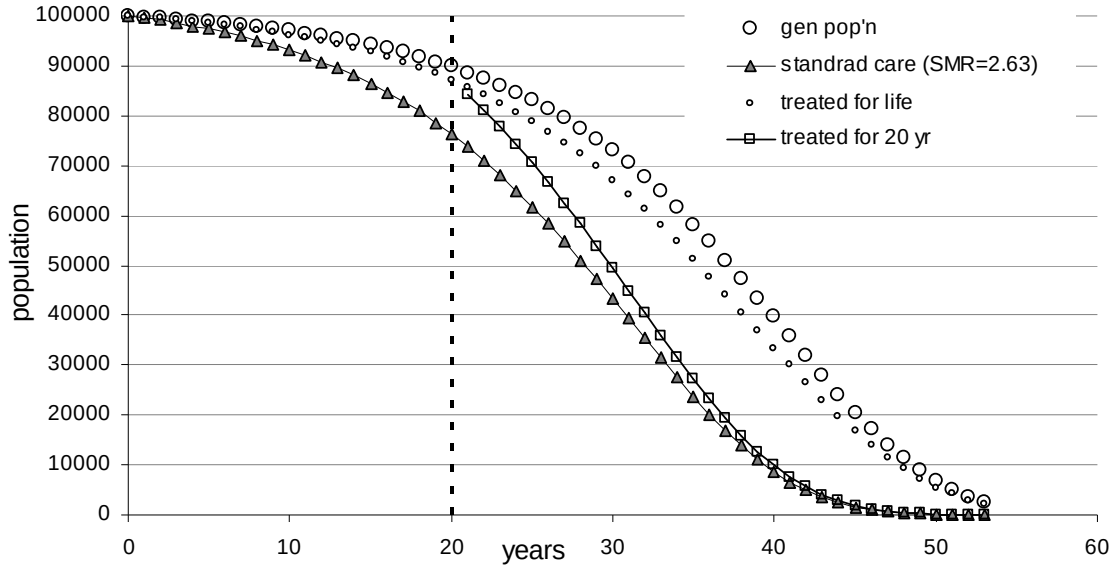

Figure 16 WMTA base case survival with treatment for 20 years or for life time

For sensitivity analysis early drop out in year one was 0%.

d) Patient attrition after year one. The MM did not allow for patient withdrawal from pegvisomant treatment. The WMTA base case assumed 20% withdrawal from pegvisomant in year one. In the absence of evidence on withdrawal rate after one year it was assumed that this was 1%. Sensitivity analysis varied this from 0% to 20%. Survival profiles at different attrition rates are shown below.

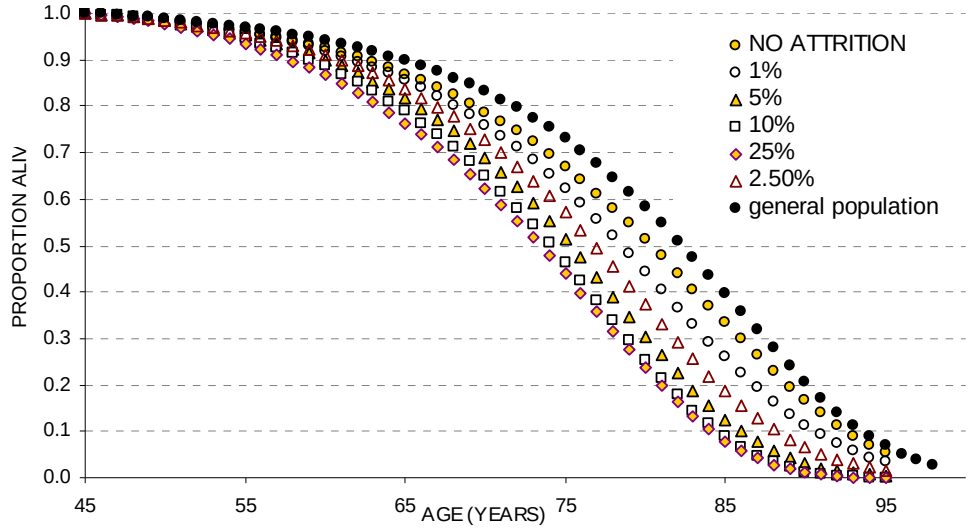

Figure 17 Base case with different rates of patient attrition after year one

e) Effectiveness of pegvisomant treatment: — QoL

The model assumes a direct link between lowered IGF-1 and QoL. The utility gain used in the MM (0.08) was not based on a study of acromegaly patients. At the time of the WMP assessment no informative studies had been published. Several studies are now available[67-72] but none have examined utility gain from pegvisomant treatment. All have reported poorer QoL for acromegaly patients compared to the general population. The main issue for the economic model is:

- Are IGF-1 levels correlated with health-related-QoL and thus reasonable indicators of QoL?

The reported correlations relevant to this issue are summarised in Table 7. Unfortunately correlation coefficients were incompletely reported and meta-analysis was not possible. Although studies were not wholly consistent the general direction of evidence supports a negative relationship between QoL and IGF-1 levels.

Table 7 Results in studies reporting correlation between QoL or disease state and IGF-1 level.

		STUDY					
		Webb 2006[71]	**Kauppinen-Makelin 2006[68]**	**Trepp 2005[72]**	**Hua 2006[70]**	**Biermasz 2004[69]**	**Rowles 2005[67]**
	Country	Spain	Finland	Switzerland	China	Netherlands	UK
	QoL‡ instrument(s)	AcroQol EQ-5D	15D	AcroQol	AcroQol	SF-36	AcroQol EQ-5D
	patient N	106	277	33	32	118	80
Correlation of HRQOL with active disease	direction *coefficient* *P*	NR†	NR	positive *NR* *0.01*	None¶ *NR* *0.497*	All patients in remission	None¶ *NR* *NR*
Correlation of HRQOL with IGF-1 level	direction *coefficient* *P*	negative *-0.12* *> 0.05*	negative *NR* *0.038*	negative *NR*†† *0.01*	NR	No relationship¥	NR

‡ AcroQol is a disease specific instrument (score 0 to 100%), the other instruments are generic

† In the prospective group an improved mean AcroQol score and decreased mean IGF-1 level were observed after treatment

¶ Study reported there was no relationship.

†† Regression equation after controlling for age, gender, duration of disease, size of adenoma, radiotherapy, and hypopituitism : minus 0.8% in AcroQol score per 10 ng/ml increase in IGF-1 (change in IGF-1 values with pegvisomant treatment is typically in hundreds of ng / ml).

¥ A narrow range of IGF-1 levels examined because all patients were in remission.

Only Rowles 2005 reported utility values.[67] This cross-sectional study examined UK patients amongst whom 72.5% had active disease and 27.5% were in remission. Their median utility index was 0.7 (range –0.07 to 0.92) compared with a value of 0.81 for matched members of the general public. On the basis of this data the model used an average utility gain of 0.11 for treatment with pegvisomant. In sensitivity analysis a gain of 0.15 (0.81 – 0.66) was used. This allowed for the fact that 27.5% of the patients in the study of Rowles 2005 were in remission so that the utility of 0.7 may have over-estimated the utility of the population licensed for pegvisomant.[67]

A summary of the input parameters for estimating the effectiveness of pegvisomant treatment is provided in Table 8.

Table 8 WMTA model input parameters for estimating effectiveness

	INPUT PARAMETER	Base Case	Sensitivity analysis	Data source / notes
(a)	Life table for general population	Equal mix English males and females aged from 45 years	Not changed	Government Actuary's department[73]
(b)	Life table standard care	SMR 2.63 applied to (a).	SMR 3.22; 3.6	Bates 1993[13] Meta-analysis
(c)	Life table pegvisomant treatment	As (a) for compliant patients, as (b) for non compliant patients		Assumed
(d)	Usual care utility	0.7	0.66; 0.60	Rowles[67]
(e)	Utility patients compliant with pegvisomant treatment	0.81		Rowles[67]
(f)	Utility patients non-compliant with pegvisomant treatment	As (d)	0.66; 0.6	Assumed
(g)	Withdrawal from pegvisomant during year one	20%	0%, 5%, 10%	Colao 2006[54]
(h)	Withdrawal from pegvisomant after year one	1% / year	0%, 5%, 10%, 20%	Assumed

Benefits, like costs, were discounted at 3.5% per annum.

3.2.6 WMTA input parameters for estimation of costs

The cost of a standard care (SC) package (Table 9) was made up of:

- Acquisition cost of drugs to "control" acromegaly (Appendix 12);
- Costs for provision of tests (IGF-1) and scans (ultrasound scan of gall bladder, MRI of pituitary);
- Costs of provision of treatment for co-morbidities.

In the MM patients in SC were all treated with LASSA. According to expert clinical opinion this does not reflect likely practice in the West Midlands. Based on clinical advice it was assumed that 25% of SC patients would receive LASSAs, either Sandostatin LA® (octreotide 30 mg/month) or Somatuline autogel® (lanreotide 60 mg/month), 25% would receive LASSAs at high dose (octreotide 60 mg/month or lanreotide 120 mg/month) combined with cabergoline (0.5 mg/day), and 50% would not receive medicine specific for control of acromegaly. It was assumed that administration of LASSAs would be equally split between Sandostatin LA® and Somatuline autogel® delivered to outpatients by injection performed by a staff nurse. It was assumed that for SC patients not receiving LASSA the only costs incurred

were for treatment of co-morbidities. In the base case we assumed treatment compliance continued through the time horizon of the model (see below for sensitivity analysis).

Table 9 WMTA input data for estimating costs

INPUT PARAMETER	ANNUAL COST / PATIENT (£)	Sensitivity analysis	Data source
STANDARD CARE			
Drugs for acromegaly (50% no drug, 25% LASSA, 25% high dose LASSA + cabergoline)	8,194.23	Increase & decrease by 25%	BNF[42] Curtis & Netten[74]
Treatment for co-morbities	1,771.56		Didoni 2004[66]
Scans and lab tests	556		Clinical opinion
TOTAL	**10,521.79**		
Compliant PEGVISOMANT patient			
Acquisition cost of pegvisomant	36,536.50	Decrease by 25%	BNF[42]
Scans and lab tests compliant patient	349		Clinical opinion & NHS reference costs[75]
Treatment for comorbities compliant patient	1,609.19		Didoni 2004[66]
TOTAL	**38,494.69**		
Noncompliant PEGVISOMANT patient (after year 1 trial)			
Acquisition of standard care drug	8,194.23	Increase by 25%	BNF[42]
Scans and lab tests	312		Clinical opinion & NHS reference costs[75]
Treatment for co-morbities noncompliant patient	1,771.56		Didoni 2004[66]
TOTAL	**10,277.79**		
Extra cost incurred in first year by trialling PEGVISOMANT	14,208.13		

The cost for treatment of co-morbidities was based on a report by Didoni 2004.[66] This was a cost of illness study conducted from the perspective of the Italian Healthcare Service that found the costs for treatment of co-morbidities differed depending on whether acromegaly was controlled or uncontrolled.[66] For SC patients and for patients noncompliant with pegvisomant the co-morbidity costs for uncontrolled acromegaly were applied.

The cost of a pegvisomant treatment package was made up of:

- Acquisition cost of pegvisomant;
- Costs for provision of tests (IGF-1,liver enzymes) and scans (MRI of pituitary);
- Costs of provision of treatment for co-morbidities.

Colao[54] reported that during 12 months treatment patients conforming to the licensed indication received a mean dose of 22.5 mg pegvisomant /day (range 10 to 40 mg). Since pegvisomant vials of 10, 15 and 20 mg are available we assumed that

on average a compliant patient would use one 20 mg vial / day at a cost of £36,500 per year.

The major cost element was acquisition cost for acromegaly drugs. In sensitivity analyses this was increased by 25% for the SC package and decreased by 25% for the pegvisomant package. Also we calculated the reduction in cost of 20 mg pegvisomant vials that was necessary to bring the ICER to £30,000 / QALY at a time horizon of 20 years.

The cost of treatment for comorbidities in pegvisomant-compliant patients was based on those for acromegaly-controlled patients as estimated by Didoni 2004.

Costs associated with pegvisomant treatment included an annual MRI scan (£ 244) and laboratory tests for liver enzyme levels (3 / year at £ 5 each) and IGF-1 (3 x £30).

Table 9 summarises input parameters for estimating the costs. Costs, like benefits, were discounted at 3.5% per annum.

According to expert clinical advice many UK patients who would be eligible for pegvisomant would likely to have previously received radiotherapy. For some of these medical treatments specific for acromegaly might cease after 5 to 10 years because the therapeutic benefits of radiotherapy would then have taken effect making medication with SSAs or pegvisomant redundant. Thus after 5 to 10 years for some patients, those in whom radiotherapy was effective, the only costs might be those incurred for co-morbidities (with a large contribution from radiation induced hypopituitarism) and disease monitoring. In both the pegvisomant and comparator patient cohorts the proportions of patients stopping medical therapies and requiring hormone replacement for hypopituitarism would be the same. Therefore a sensitivity analysis was conducted in which no costs for SSA or pegvisomant were incurred after 7.5 years for 50% of patients.

3.2.7 Cost effectiveness results (base case)

The incremental utility, life years and costs, together with ICERs at 20 years are shown in Table 10 and are compared with previous estimates in Table 11.

Table 10 Incremental cost effectiveness ratios, base case at 20 years

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Standard care	142,507		9.48		
Pegvisomant	443,329	300,822	11.00	1.51	198,621
Strategy	**Cost**	**Cost difference**	**Life years**	**Life years difference**	**ICER (£/LYG)**
Standard care	142,507		13.54		
Pegvisomant	443,329	300,822	14.06	0.52	578,004

Table 11 Estimates of cost effectiveness of pegvisomant

MODEL	ICER (£/QALY)	ICER (£/LYG)
WMTA	198,621	578,004
Manufacturer	105,119	194,349
WMP		748,480

3.2.8 Cost effectiveness results (sensitivity analyses)

The following effectiveness parameters were changed in sensitivity analyses: patient attrition from pegvisomant treatment after year one (% lost / year); survival in SC (changed SMR); utility in SC; withdrawal from pegvisomant treatment in year one (% of patients). Sensitivity analysis included increasing acquisition costs for standard care and decreasing those for pegvisomant, it also included varying the time horizon from the base case (20 years) to 5, 10, 30, 40, and 50 years. The results are summarised in Table 12. These results indicate that the base case ICER values are reasonably robust to parameter changes. In sensitivity analysis over a 20 year time horizon no ICER reduced below £119,000 / QALY. With longer time horizons (beyond 30 years) the lowest £/QALY value was 89,000.

Table 12 Sensitivity analyses (results for time horizon 5 to 50 years, and for 20 years)

	Range	5-50 yrs £ / QALY			20 yr £ / QALY	5-50 yrs £ / LYG		
	BASE CASE	***248,542***	***to***	***141,003***	***198,621***	***3,329,652***	***to***	***206,683***
Survival in SC	SMR 3.22	244,234	to	127,895	184,688	2,451,497	to	168,310
	SMR 3.6	241,132	to	120,685	175,827	2,050,193	to	150,368
Utility SC	0.66	185,251	to	121,273	157,333	3,329,652	to	206,683
	0.60	134,048	to	100,234	119,936	3,329,652	to	206,683
0 %/yr attrition after year 1	SC utility 0.7	248,514	to	136,664	198,813	3,364,137	to	193,249
	SC utility 0.66	185,199	to	118,289	157,410	3,364,137	to	193,249
	SC utility 0.60	133,992	to	98,437	119,943	3,364,137	to	193,249
10 %/yr attrition after year 1	SC utility 0.7	248,911	to	169,256	198,305	3,033,612	to	322,329
	SC utility 0.66	185,828	to	140,000	157,535	3,033,612	to	322,329
	SC utility 0.60	134,643	to	111,175	120,403	3,033,612	to	322,329
20 %/yr attrition after year 1	SC utility 0.7	249,605	to	181,773	199,986	2,735,880	to	389,872
	SC utility 0.66	186,723	to	148,228	159,070	2,735,880	to	389,872
	SC utility 0.60	135,514	to	116,092	121,716	2,735,880	to	389,872
Year 1 loss from pegvisomant	0%	241,797	to	140,036	196,745	3,239,282	to	205,266
SC drug costs	Increased by 25%	231,045	to	132,671	185,181	3,095,246	to	194,470
PEG drug costs	Decreased by 25%	169,844	to	97,620	135,558	2,275,349	to	143,092
SC drug costs PEG drug costs	Increased by 25% Decreased by 25%	152,347	to	89,288	122,118	2,040,944	to	130,879
PEG = pegvisomant. SC = standard care. SMR = standardised mortality ratio.								

In order to reduce the ICER (£/QALY) to 30,000 at 20 years in the base case scenario it would be necessary to reduce the price of the pegvisomant package of care from £38,495 / patient / year to about £14,000 / patient / year; if this were achieved only by reduction in cost of pegvisomant vials the price of these would need to fall from £100 / 20 mg vial to approximately £33 / 20 mg vial.

3.2.9 Sensitivity analysis: perfect drug scenario

In order to further explore the cost effectiveness of pegvisomant we set all input parameters to greatly favour the intervention relative to SC. In particular in this analysis all patients receiving the SC package are prescribed LASSAs (care package cost £18,326 / year / patient). The SC SMR relative to the general population was taken as 3.6 and SC utility at 0.6; all patients were retained in pegvisomant treatment which returned survival and utility to that of the general public. It follows from these results (Table 13) that it is extremely unlikely that the

ICER of pegvisomant versus SC could fall below £70,000 / QALY even over a greatly extended time horizon of 50 years.

Table 13 ICER values in perfect drug scenario

TIME HORIZON	£/QALY	£/LYG
5 YEARS	97,147	1,538,483
10 YEARS	92,568	675,311
20 YEARS	85,235	282,286
30 YEARS	78,504	168,540
40 YEARS	74,138	129,201
50 YEARS	72,957	120,962

3.2.10 Summary of economic analysis

- We adapted a decision tree model to assess the cost-effectiveness of pegvisomant compared to standard care for the treatment of acromegaly patients whose IGF-1 had failed to normalise using other treatments. The model was designed to estimate costs and outcomes, in terms of QALYs and LYG, from the perspective of the NHS over time horizons up to 50 years.
- According to this model pegvisomant treatment is unlikely to be cost effective compared with standard care when judged according to generally applied value-for-money criteria. This finding was robust to sensitivity analyses.

4. FACTORS RELEVANT TO NHS

According to expert clinical opinion ~ 5% TO 10% of all acromegaly patients fail to normalise after all available current treatments have been tried other than pegvisomant; in the West Midlands, assuming a prevalence of 58 / million population, this represents about 15 to 30 patients. Assuming that all the patients in the West Midlands eligible for pegvisomant according to licensed indication (about 30) were placed immediately onto a pegvisomant regime then, if they were all compliant with treatment, the resulting increase in budget would be about £850K per year. If pegvisomant was to be introduced in a less discriminate way so that it was used for patients whose IGF-1 could be normalised using much cheaper treatments, increased expenditure would rapidly escalate to several millions.

To place the intervention in a wider context it should be recognised that although acromegaly is insufficiently rare to be classified as an ultra-orphan disease it does qualify as an orphan disease and both SSAs and pegvisomant are classified as orphan drugs. The population licensed for pegvisomant treatment represents only about 5% of the total patients with acromegaly; this sub-group of “unresponsive patients” fulfils the numerical criterion for ultra-orphan status. As such some people might consider or argue that pegvisomant would be wholly or partially exempt from widely used criteria for deciding on the value-for-money of an intervention. The National Specialist Commissioning Advisory Group (NSCAG) has already developed policy on the provision of a number of expensive orphan drugs, such as those used in the treatment of several lysosome-storage diseases.[76] Some of these drugs have been estimated to exhibit extremely high ICERs; examples include £252K / QALY for Fabrazyme used in the treatment of Fabry’s disease, and £380 to £470K / QALY for Cerezyme used in the treatment of Gaucher’s disease.[77,78] The sustainability of funding policies in the face of increasingly numerous approvals by licensing authorities of very expensive orphan drugs has been debated.[79,80] Questions of equity may arise for decision makers when comparisons are made between the cost-effectiveness estimates of different orphan drugs, or between the estimates for orphan drugs and those for conventional drugs. This is currently an area of great debate within health commissioning both nationally and internationally.

5. DISCUSSION

5.1 Main clinical effectiveness results

One moderate to good quality RCT with 12 weeks follow up provided evidence that pegvisomant is highly effective for normalising IGF-1 levels in patients with acromegaly. This finding was backed up by a considerable number of non-randomised studies some of which extended observation up to one year and a little beyond. The RCT provided evidence that some signs and symptoms of the disease are relieved with pegvisomant treatment, other studies reported results that generally supported this finding but were not wholly consistent. On average, pegvisomant treatment raises GH levels about two fold necessitating intermittent MRI monitoring for potential tumour progression. In a few patients pegvisomant induces adverse increases in liver enzyme levels that may temporarily or permanently necessitate withdrawal from treatment. There was a paucity of good evidence relating to patient compliance and treatment safety that extended beyond one year, and no studies were found that reported on the impact of pegvisomant on health related quality of life.

5.2 Main cost-effectiveness results

One economic assessment was identified. This reported the manufacturer's estimate of cost effectiveness to be £105,119 / QALY and £194,349 / LYG over a 20 year time horizon. The authors of the assessment estimated an ICER of £748,480 / LYG. A modified version of the manufacturer's decision analytical model was developed in order to obtain an improved estimate of the cost-effectiveness of pegvisomant. This delivered an ICER of £198,621 / QALY and £577,203 / LYG. These estimates were reasonably robust in the face of extensive sensitivity analyses. To achieve an ICER of £30,000 / QALY under base case model conditions a substantial reduction in the price of pegvisomant would be required from £100 per 20 mg vial to £33 / 20 mg vial. Applying a perfect drug scenario in which all model parameters were selected so as to strongly favour pegvisomant delivered an ICER of £85,235 / QALY and £282,286 / LYG over a 20 year time horizon.

5.3 Strengths and limitations

Strengths

The review of clinical effectiveness synthesised evidence from all reasonably sized studies, rather than rely solely on the single RCT which may not have examined patients exactly matching the population identified in the licensed indication.

The strengths of the WMTA adaptation of the manufacturer's decision analytical model include the following aspects.

- Allowance was made for patient non-compliance and transfer of patients from pegvisomant to standard care (SC).
- The cost inputs for SC and pegvisomant treatment packages were estimated with more relevance to the West Midlands.
- Mortality rates were based on a synthesis that considered data from numerous studies rather than from a single study and a pooled meta-analytic estimate was used in sensitivity analysis
- Utility deficit resulting from acromegaly was based on QoL measures made in patients with acromegaly rather than on patients that experience a coronary event
- Extensive sensitivity analyses were undertaken

Limitations

For the review of clinical effectiveness a comprehensive recovery of conference abstracts was not attempted. Examination of the abstracts recovered made it unlikely that any significant studies have been missed, but this possibility cannot be wholly ruled out.

The economic assessment has the following limitations

- There is no evidence on which to base utility gained from treatment with pegvisomant. The assumption was made that utility is fully returned to that of the general population; this will tend to underestimate the ICER and overestimate cost effectiveness.

- There is no evidence upon which to base the survival gain experienced by patients receiving pegvisomant. The assumption was made that survival is returned to that for the general population; this will tend to underestimate the ICER and overestimate cost effectiveness.
- The costs for treatment of co-morbidities was based on an Italian retrospective cost of illness study. These findings may not bereliably generalisable to the West Midlands. Furthermore costs associated with some sequalae of unsuccessfully controlled acromegaly, such as surgery for joint problems, dentistry, carpel tunnel syndrome and prognathism, may have been ignored; some of these costs may be avoided with pegvisomant treatment. The complete lack of any empirical evidence on event rates precluded consideration of these costs.

5.4 Further research

There are clear requirements for further research directed at identifiable uncertainties regarding the effectiveness and cost effectiveness of pegvisomant. These include:

1. Extended follow up studies are required. These should monitor the maintenance of response with regard to IGF-1 and GH levels, treatment safety especially with regard to tumour progression and induction of liver enzymes or other potential adverse events. Follow up studies so far conducted appear to suffer from selection bias making reliable conclusions impossible. The rarity of the disease means that such studies would be best pursued at the level of a national or large regional registry; particular attention is required with respect to completeness of follow up and recording of reasons for withdrawal from treatment and transfer to other treatments.
2. There is a need for quality of life studies that allow estimation of any patient centred health improvement that may be induced by pegvisomant. These should be conducted using both disease specific instruments (e.g. AcroQoL) and generic instruments (e.g. EQ-5D).

3. Several small non-randomised studies have explored the possibility that therapy combining LASSAs and low dose or reduced frequency pegvisomant may be as effective as pegvisomant alone and also cheaper. The reduced frequency of subcutaneous injection might improve compliance. This needs to be pursued in a properly controlled randomised study. Trials are currently underway but have not yet reported their findings.
4. Elsewhere in Europe and in the USA pegvisomant is being used as an alternative intervention to radiotherapy. The avoidance of hypopituitarism expected as a consequence of this alternative treatment strategy would be expected to have an impact on costs, QoL and survival. Economic analysis is require to assess the cost effectiveness of this strategy.
5. Economic models need to be updated as new information accrues. It is unlikely however that the uncertainties about patient survival in and out of pegvisomant treatment will diminish.

6. CONCLUSIONS

Pegvisomant treatment for acromegaly is highly effective for improving patients' IGF-1 level which is widely accepted as an important indicator of disease status. This conclusion is based on evidence from a single RCT and a considerable number of small non-randomised before and after studies. Evidence is lacking about the long term effects of treatment with respect to improved signs and symptoms of disease, quality of life, patient compliance and safety. An economic evaluation using a simple decision tree model indicated that pegvisomant was very unlikely to represent good value for money according to currently applied standards. The prevalence of acromegaly (~58 / 10^6) falls just outside the definition for an ultra-orphan disease (< 20 / 10^6) but within the orphan disease criterion; thus pegvisomant is an acknowledged orphan drug and as such might be considered by some policy or decision makers to be wholly or partially exempt from normally applied-value-for-money criteria and subject to other criteria as yet ill defined or incompletely applied by national or local reimbursement agencies.

7. APPENDICES

Appendix 1 Literature search strategies

1] EFFECTIVENESS. The following data bases were searched using the listed strategies.

Database: Cochrane Library (Wiley) 2007 Issue 1
Search strategy

#1 pegvisomant
#2 somavert
#3 growth next hormone next receptor next antagonist*
#4 b2063
#5 #1 or #2 or #3 or #4
#6 acromegaly
#7 exp acromegaly/
#8 #6 or #7
#9 #5 and #8

Database: MEDLINE(Ovid) 1950 to March Week 3 2007
Search strategy

1 pegvisomant.mp.
2 somavert.mp.
3 b2036.mp.
4 growth hormone receptor antagonist$.mp. or exp growth hormone receptor antagonist/
5 or/1-4
6 acromegaly.mp. or exp ACROMEGALY/
7 (systematic adj review$).tw.
8 (data adj synthesis).tw.
9 (published adj studies).ab.
10 (data adj extraction).ab.
11 meta-analysis/
12 meta-analysis.ti.
13 comment.pt.
14 letter.pt.
15 editorial.pt.
16 animal/
17 human/
18 16 not (16 and 17)
19 5 not (13 or 14 or 15 or 18)
20 or/7-12
21 19 and 20

Database: MEDLINE(Ovid) 1950 to March Week 3 2007
Search Strategy:

1 pegvisomant.mp.
2 somavert.mp.
3 growth hormone receptor antagonist$.mp.
4 b2036$
5 or/1-4
6 acromegaly.mp. or exp ACROMEGALY/
7 6 and 5

Database: MEDLINE (Ovid) In-Process & Other Non-Indexed Citations April 3 2007
Search Strategy

1 pegvisomant.mp.
2 somavert.mp.
3 growth hormone receptor antagonist$.mp.
4 b2036$
5 or/1-4
6 acromegaly.mp. or exp ACROMEGALY/
7 5 and 6

Database: EMBASE (Ovid) 1980 to 2007 Week 13
Search Strategy:

1 pegvisomant.mp. or exp PEGVISOMANT/
2 somavert.mp.
3 growth hormone receptor antagonist$.mp.
4 b2036$
5 or/1-4
6 acromegaly.mp. or exp ACROMEGALY/
7 5 and 6

Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature (EBSCO) 1982 to April 4 2007
Search Strategy:

1 pegvisomant.mp.
2 somavert.mp.
3 growth hormone receptor antagonist$.mp.
4 b2036$
5 or/1-4

Additional sources searched for abstracts, proceedings and ongoing research:

ENDO 2005, 2006 (Endocrine Society's 87th and 88thAnnual Meeting 2005,2006) , ZETOC (British Library database including proceedings); NRR 2007 Issue 1, Clinical Trials.gov as at April 2007. Terms used taken from Cochrane Library search strategies.

2] Cost effectiveness and other searches :

Database: MEDLINE(Ovid) 1950 to March Week 3 2007
Search Strategy: Cost searches

1 pegvisomant.mp.
2 somavert.mp.
3 b2036$.mp.
4 growth hormone receptor antagonist$.mp. or exp growth hormone receptor antagonist/
5 or/1-4
6 acromegaly.mp. or exp ACROMEGALY/
7 5 and 6
8 economics/
9 exp "costs and cost analysis"/
10 cost of illness/
11 exp health care costs/
12 economic value of life/
13 exp economics medical/
14 exp economics hospital/
15 economics pharmaceutical/
16 exp "fees and charges"/
17 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
18 (expenditure$ not energy).tw.
19 (value adj1 money).tw.
20 budget$.tw.
21 or/8-20
22 7 and 21

Database: MEDLINE(Ovid) 1950 to March Week 3 2007
Search Strategy: Economic modelling searches

1 pegvisomant.mp.
2 somavert.mp.
3 b2036$.mp.
4 growth hormone receptor antagonist$.mp. or exp growth hormone receptor antagonist/
5 or/1-4
6 acromegaly.mp. or exp ACROMEGALY/
7 5 and 6
8 decision support techniques/
9 markov.mp.
10 exp models economic/
11 decision analysis.mp.
12 cost benefit analysis/
13 or/8-12
14 7 and 10
15 7 and 13

Also searched : NHS EED Cochrane Library (Wiley) 2007 Issue 1, OHE HEED April 2007 Issue (see Cochrane Library search strategy for terms used)

Database: MEDLINE (Ovid) 1950 to March Week 3 2007
Search Strategy: Side effects /quality of life

1 pegvisomant.mp.
2 somavert.mp.
3 growth hormone receptor antagonist$.mp.
4 b2036$
5 or/1-4
6 acromegaly.mp. or exp ACROMEGALY/
7 5 and 6
8 side effect$.mp.
9 adverse effect$.mp.
10 adverse event$.mp.
11 or/8-10
12 7 and 11
13 quality of life/
14 life style/
15 health status/
16 health status indicators/
17 or/13-16
18 7 and 17
19 5 and 17
20 6 and 17
21 or/18-20

Database: EMBASE (Ovid) 1980 to 2007 Week 13
Search Strategy: Quality of life

1 acromegaly.mp. or exp ACROMEGALY/
2 quality of life.mp. or exp "Quality of Life"/
3 exp Lifestyle/
4 exp Health Status/
5 exp Health Survey/
6 or/2-5
7 1 and 6

Appendix 2 List of excluded studies with reasons for exclusion

Fourteen full text papers were excluded. These are listed in Table 14 below together with reasons for exclusion.

Table 14 Studies excluded after examination of full texts

REFERENCE	REASON FOR EXCLUSION
Trainer PJ, Drake WM, Perry LA, Taylor NF, Besser GM, Monson JP. Modulation of cortisol metabolism by the growth hormone receptor antagonist pegvisomant in patients with acromegaly. The Journal of clinical endocrinology and metabolism 2001; 86(7):2989-2992	Less than 10 patients
Herman-Bonert VS, Zib K, Scarlett JA, Melmed S. Growth hormone receptor antagonist therapy in acromegalic patients resistant to somatostatin analogs. The Journal of clinical endocrinology and metabolism 2000; 85(8):2958-2961.	Less than 10 patients
Galland F, Kamenicky P, Affres H, Reznik Y, Pontvert D, Le BY et al. McCune-Albright syndrome and acromegaly: effects of hypothalamopituitary radiotherapy and/or pegvisomant in somatostatin analog-resistant patients. Journal of Clinical Endocrinology & Metabolism 2006; 91(12):4957-4961.	Less than 10 patients
Main KM, Sehested A, Feldt-Rasmussen U, Main KM, Sehested A, Feldt-Rasmussen U. Pegvisomant treatment in a 4-year-old girl with neurofibromatosis type 1. Hormone Research 2006; 65(1):1-5.	Less than 10 patients
Lansang C, Chitaia N, Simpson NE, Kennedy L, Lansang C, Chitaia N et al. Serum IGF-1 in treated acromegaly - how normal is "normal"? Pituitary 2005; 8(2):135-138.	Less than 10 patients
Muller AF, van der Lely AJ, Muller AF, van der Lely AJ. Pharmacological therapy for acromegaly: a critical review. Drugs 2004; 64(16):1817-1838.	Not primary study or systematic review
Colao A, Pivonello R, Cappabianca P, Auriemma RS, De Martino MC, Ciccarelli A et al. The use of a GH receptor antagonist in patients with acromegaly resistant to somatostatin analogs. Journal of Endocrinological Investigation 2003; 26(10 Suppl):53-56.	Not primary study or systematic review
Trainer PJ, Trainer PJ. Lessons from 6 years of GH receptor antagonist therapy for acromegaly. Journal of Endocrinological Investigation 2003; 26(10 Suppl):44-52.	Not primary study or systematic review
Drake WM, Rowles SV, Roberts ME, Fode FK, Besser GM, Monson JP et al. Insulin sensitivity and glucose tolerance improve in patients with acromegaly converted from depot octreotide to pegvisomant. European Journal of Endocrinology 2003; 149(6):521-527.	Less than 10 patients
Burt MG, Ho KK, Burt MG, Ho KKY. Comparison of efficacy and tolerability of somatostatin analogs and other therapies for acromegaly. . Endocrine 2003; 20(3):299-305.	Not primary study or systematic review
Rose DR, Clemmons DR, Rose DR, Clemmons DR. Growth hormone receptor antagonist improves insulin resistance in acromegaly. Growth Hormone & Igf Research 2002; 12(6):418-424.	Less than 10 patients
Drake WM, Parkinson C, Akker SA, Monson JP, Besser GM, Trainer PJ et al. Successful treatment of resistant acromegaly with a growth hormone receptor antagonist. European Journal of Endocrinology 2001; 145(4):451-456.	Less than 10 patients
van der Lely AJ, Muller A, Janssen JA, Davis RJ, Zib KA, Scarlett JA et al. Control of tumor size and disease activity during cotreatment with octreotide and the growth hormone receptor antagonist pegvisomant in an acromegalic patient. Journal of Clinical Endocrinology & Metabolism 2001; 86(2):478-481.	Less than 10 patients
Grottoli S, Gasco V, Mainolfi A, De GD, Ghigo E. Positive metabolic impact of treatment with pegvisomant in an acromegalic patient. Hormone Research 2007; 67 Suppl 1:174-176.	Less than 10 patients

Appendix 3 Details of included studies

Study / Reference Region / Country	Design of Study / Country	Population with acromegaly					Intervention *subcutaneously daily unless otherwise stated*	Comp.	F/up	Main Outcomes
		Inclusion Criteria	**Exclusion Criteria**	**N**	**Previous Treatments (% by group)**	**Age / sex / other reported**				
Trainer 2000[46] (Germany, Netherlands, Sweden, UK, and US)	Multicentre, Double-blind, placebo-controlled RCT of three different daily doses of pegvisomant (10, 15, or 20 mg) and placebo	Diagnosis of acromegaly on basis of signs and symptoms, pituitary adenoma on computed tomography or magnetic resonance imaging (MRI), and high IGF-1 Serum IGF-1 concentration at the second screening visit (off any previous medications for acromegaly) at least 1.3 times the upper limit of the age-adjusted normal range	Treatment with a long-acting somatostastin analog within 12 weeks before enrollment	112	Surgery: Placebo 10 mg 15 mg 20 mg 26(81%) 22(85%) 22(85%) 23(82%) Radiotherapy placebo 10 mg 15 mg 20 mg 17(53%) 11(42%) 14(54%) 15(54%) SS analogue placebo 10 mg 15 mg 20 mg 17 (53%) 15(58%) 9 (35%) 14(50%)	*Mean Age:* placebo 10 mg 15 mg 20 mg 50 47 46 48 *Sex M/F* placebo 10 mg 15 mg 20 mg 19/13 15/11 14/12 15/13 *Duration of Acromegaly:* Placebo 10 mg 15 mg 20 mg 8±8y 8±7 8±7 8±7	*N=26, 26, 28* *Drug:* pegvisomant *Dose 10, 15, 20* mg daily *Regime*, day 1 an 80 mg loading dose	*placebo N = 32*	12 weeks	- Percentage change in serum IGF-1 concentration from base line. - Free IGF-1, growth hormone (GH), IGF binding protein-3 (IGFBP-3), acid-labile subunit of IGFBP-3, ring size of the fourth (or fifth, if fourth finger too large) digit of right hand, scores for signs and symptoms (0 = No symptoms; 8 = Severe, symptoms) - Anti-GH antibodies, - hematology, serum chemistry, urinalysis, - adverse events, - tumor volume determined on MRI of pituitary, electrocardiogram

Study / Reference Region / Country	Design of Study / Country	Population with acromegaly					Intervention *subcutaneously daily unless otherwise stated*	Comp.	F/up	Main Outcomes
		Inclusion Criteria	Exclusion Criteria	N	Previous Treatments (% by group)	Age / sex / other reported				
Van der Lely 2001[55] (Germany, Netherlands, Sweden, UK, US) This study is a subset of Trainer 2000	This study is an extension to the Trainer 2000 but it is now an open-label, uncontrolled, observational, dose-titration study following placebo-controlled clinical trials	Serum IGF-1 concentration at least 1.3 times the upper limit of the age-adjusted normal range at the second screening visit (at least 2 weeks after discontinuation of somatostastin analogs and at least 5 weeks after discontinuation of dopamine agonists)	None stated	167	treatment / 6 mo / 12 mo / 18 mo surgery 111(85) 82(91) 35(90) X ray 78(60) 57(63) 26(67) SS 97(74) 74(82) 33(85) DA 67(51) 48(53) 19(48)	*Mean Age* *6 mo n=131 46±14* *12 mo n=90 44±13* *18 mo n=39 42±13* *% M Sex* *6 mo n=131 75(57)* *12 mo n=90 47(52)* *18 mo n=39 18(46)* *Duration of Acromegaly*: *6 mo n=131 8(8)* *12 mo n=90 8(7)* *18 mo n=39 8(8)*	*N=167 but only 152 received daily dosing* *Drug pegvisomant* *Dose* Pegvisomant dose, mean ± SE (mg/d) *6 mo n=131* 14.7 ± 0.4 *12 mo n=90* 18.0 ± 0.7 *18 mo n=39* 19.6 ± 1.4	*NA*	18-month	- Mean serum IGF-1 and GH concentrations at baseline -Mean pituitary volume -Fasting serum insulin concentrations - Adverse events

Study / Reference Region / Country	Design of Study / Country	Population with acromegaly					Intervention *subcutaneously daily unless otherwise stated*	Comp.	F/up	Main Outcomes
		Inclusion Criteria	Exclusion Criteria	N	Previous Treatments (% by group)	Age / sex / other reported				
Fairfeild 2002[48] Multicenre trial This study is a subset of Trainer 2000	RCT placebo controlled but serum was available from Trainer 2000	Aged 18 years or more, clinical symptoms and signs of acromegaly, radiographic evidence of pituitary adenoma and IGF greater than 1.3 times the upper limit of age and sex-specific normal range.	Exclusion if did not meet: 2 weeks discontinuation of short SS, 5 weeks discontinuation dopamine agonist, of 12 weeks after discontinuation long acting SS	27	Not reported	*Mean Age* *45.2±2.7 pegvisomant vs 45.2±5.1* *F/M Sex: 10/10 in pegvisomant vs 2/5 placebo* *Duration of Acromegaly*: not stated	*N=20* *Drug pegvisomant* *Dose 10, 15, 20 mg / day*	*vs placebo N=7*	12 weeks	Serum markers of bone turnover comparing patients taking 10, 15, 20 mg pegvisomant to placebo

Study / Reference Region / Country	Design of Study / Country	Population with acromegaly					Intervention *subcutaneously daily unless otherwise stated*	Comp.	F/up	Main Outcomes
		Inclusion Criteria	Exclusion Criteria	N	Previous Treatments (% by group)	Age / sex / other reported				
Sesmilo 2002[47] Multicenre trial This study is a subset of Trainer 2000	Cross sectional Placebo controlled non random Then longitudinal study after 12 weeks	Patients included following standard clinical and biochemical criteria and confirmed by imaging technique. IGF-I is 30% or greater above matched above the adjusted upper limit of the normal range.		47	Not stated	*Mean Age 45.±12 pegvisomant vs 45.±10* *F/M Sex: 23/25 ve 26/18 control*	*Daily pegvisomant for 12 weeks for the RCT* 10 mg / *day* n=14, 15 mg / *day* n=10, 20 mg n =12. However Subsequently all patients receive at least 10 mg / *day* pegvisomant for 18 weeks.	*47 matched for age and body mass index in healthy controls* before vs after	12 weeks for RCT 18 months for the open lable	Cardio vascular risk factors before and after normalization of IGF-I GH, IGF-I Total Cholesterol HLD, LDL Total chol/HDL chol Triglyceride, CRP IL-6 Lipoprotien Homocysteine Glucose Insuline IRHOMA
Barkan 2005[64]	A multicentre open label trial Before and after gesign	Patients with acromegaly previously treated with octreotide long-acting release.	Pituitary adenoma within 3mm of the optic chiasm, severe symptomatology that require surgery known or suspected alcohol abuse	53	Surgery: 83% Radiotherapy 60% SSA 100% DopA 8% PEG 91%	*Mean age* [yr(range)] 49(23-81) Men/women[no.(%)] 27/26(51/49)	Pegvisomant 10mg /day	Measures at baseline week 0 taking octerotide	32 weeks	Glucose homeostasis Effects on IGF-I and GH Tumour volume Safety
Jorgensen 2005[60]	uncontrolled non randomised trial taking five different regimes following fixed treatment algorithm	Patients with acromegaly not responding adequately to conventional therapy	Not stated	11	Surgery: 82% Radiotherapy 45% SSA 91%	*Mean age* [yr(range)] 46 (23-71) 4 women , 7males	10 mg /day pegvisomant for 6 weeks. Then 15 mg treatment with pegvisomant for 6 weeks. Then 15 mg /d plus SMS for 12 weeks	SMS therapy alone. Off SMS therapy for 2 months	Sequential duration of 5 different regimes 2 months no treatment with SMS, 6 weeks with 10 mg /d PEG, 6 weeks treatment with 15 mg/d ;12 wks SMS + PEG 15 mg/d.	Fasting glucose and glucose tolerance test IGF-I GH

Study / Reference Region / Country	Design of Study / Country	Population with acromegaly					Intervention *subcutaneously daily unless otherwise stated*	Comp.	F/up	Main Outcomes
		Inclusion Criteria	Exclusion Criteria	N	Previous Treatments (% by group)	Age / sex / other reported				
Feenstra 2005[59]	Prospective Open label Single centre. Before and after combined therapy	Patients with active acromegaly who are not controlled with long acting SMS analogue	Not stated	26	Surgery: 15% Radiotherapy & surgery 31%% Neither radiotherapy or surgery 54%	*Mean (SD, range) 51 (12.6, 31-79)* *Male 15(58%)*	Long acting SSA (monthly) + PEG once / wk titrated from 25 mg per week until normalisation of IGF-1. until a weekly dose reached 80 mg.	Somatostatin before combined therapy	42 weeks	IGF-I Liver enzymes
Parkinson 2003 a[53] This study is a subset of Trainer 2000	Controlled non RCT	15 patients with an establishes diagnosis acromegaly were taken from an RCT (Trainer 2000) And one from van der Lely 2001)	Not stated	16	Surgery: 81% Radiotherapy 75%	Median age 52 yr range [28-78y] Male 9/16	10 mg / *day* pegvisomant with dose increments of 5 mg / *day* every 8 weeks until serum IGF-1 was in the age related reference range Median dose 20 mg/d range 10-40 mg / *day*	32 age and sex matched ambulatory individuals	Mean 7 months Range [3-11]	IGF-I Markers of bone turnover: PIIINP OC CTx PINP BAP Tx/Cr ratio
Parkinson 2003 b[63] This study is a subset of Trainer 2000	Before and after design	15 patients with an establishes diagnosis acromegaly were taken from an RCT (Trainer 2000) & one from van der Lely 2001)	Not stated	16	Surgery: 81% Radiotherapy 75%	Median age 52 yr range [28-78y] Male 9/16	10 mg / *day* pegvisomant with dose increments of 5 mg/ *day* every 8 weeks until serum IGF-1 was in the age related reference range	*Measures at baseline*	Mean 7 months Range [3-11]	Serum leptin Fasting plasma insulin Fasting plasma glucose

Study / Reference Region / Country	Design of Study /	Population with acromegaly					Intervention *subcutaneously daily unless otherwise stated*	Comp.	F/up	Main Outcomes
		Inclusion Criteria	Exclusion Criteria	N	Previous Treatments (% by group)	Age / sex / other reported				
Parkinson 2002[62] (UK) Most a subset of Trainer 2000	Two centres, Before and after design	Diagnosis of acromegaly Serum IGF-1 at least 1.3 x the upper limit of the age-adjusted normal range SSA and DopA washout 2 and 5 weeks	Treatment with lipid lowering drugs	20	Surgery: 70% Radiotherapy 60% Medical only 15%	*Mean Age: yrs* mean range 58.7 28 to 79 *Sex M/F* 45% / 55% *Duration of Acromegaly:* Unclear	from 10 mg / day to normalisation of IGF-1 (dose change every 8 weeks as necessary)	baseline vs after IGF-1 normal	mean duration 10 months	base line. vs at normalisation of IGF-1 - serum IGF-1 -total chol; HDL-chol; LDL-chol; apo B; apo A1; TG; Lipo *a;* glucose; insulin; insulin resistance.
Parkinson 2004[52] (UK) 15 of 16 a subset of Trainer 2000	Single centre, Uncontrolled before and after design	Diagnosis of acromegaly Serum IGF-1 at least 1.3 x the upper limit of the age-adjusted normal range SSA and DopA washout 2 and 5 weeks		16	Surgery: NR Radiotherapy NR Just prior to PEG SSA DopA 31% 50%	*Median Age: yrs* median range 52 27 to 58 *Sex M/F* 56% / 44% *Duration of Acromegaly:* Unclear	from 10 mg / day to normalisation of IGF-1 (dose change every 8 weeks as necessary) mean dose 15 mg / day range 10 to 40	baseline vs after IGF-1 normal	mean duration 7 months range 3 -11	base line. vs at normalisation of IGF-1 IGF-1 IGF binding proteins 1 , 2 & 3 terniary complex-associated IGFBP-3
Jehle 2005[56] (US)	Single centre, Uncontrolled before and after design	Diagnosis of acromegaly and serum IGF-1 not normalised by SSA therapy. Medications for acromegaly withdrawn at least 4 wks prior to PEG		10	Surgery: 100% Radiotherapy 30% Medical SSA / Dop A PEG 80% 20%	*Age: yrs* mean range 50 39 to 67 *Sex M/F* 70% / 30% *Duration of Acromegaly:* Mean range 8.6 years 1-24	40 on day 1, then 10 mg / *day* and then titrated from 10 until IGF-1 normal & then frequency adjusted to least required for stable normal IGF-1. BEFORE vs AFTER mean dose 15 mg / day range 10 to 40	dose repeats required for IGF-1 normal vs baseline	duration range 12 - 20	base line. and dose frequency for normalisation of IGF-1

Study / Reference /Country	Design of Study / Country	Population with acromegaly					Intervention *subcutaneously daily unless otherwise stated*	Comp.	F/up	Main Outcomes
		Inclusion Criteria	**Exclusion Criteria**	**N**	**Previous Treatments (% by group)**	**Age / sex / other reported**				
Paisley 2006[51] (UK) Cases a subset from Trainer 2000	Probably single centre, before and after design case (n=20) : control (n=25) study	Diagnosis of acromegaly Serum IGF-1 at least 1.3 x the upper limit of the age-adjusted normal range SSA and DopA washout 2 and 5 weeks	Treatment with a long-acting somatostastin analog	20	Surgery: 80% Radiotherapy 80% SSA unclear	*Age: yrs* *Acromegaly* mean 56.1, SD 13.8; *control subjects* mean 56.6, SD 13.8 *Sex M/F* *Acromegaly* 55% / 45%; *control subjects* 52% / 48% *Duration of Acromegaly:* Unclear	*Regime* daily, subcutaneously. Day 1: a 80 mg loading dose, then from 10 mg / day titrated every 8 wks by 5 mg / day as necessary to provide IGF-1 normality. Dose range 10 to 60 mg / day	baseline vs after IGF-1 normal cases vs controls	mean duration not reported *"up to more than one year"*	cases vs controls for base line. vs at normalisation of IGF-1 Serum IGF-1 CVD markers**:** Matrix metallo- proteinase, endothelial growth factor, Total chol:, TG, glucose.
Biering 2006[49] (Germany)	multicentre retrospective case series	Acromegaly receiving PEG in Germany march 2003 to end 2004. "Most" only treated with PEG if SSA failed to normalise IGF-1	Not reported	142	Not reported	Not reported	Dose not reported Mean dose duration 28.3 mg */ day* [SD 19.9] weeks.	baseline vs treatment	Max 21 months	Analysis of 12 patients that developed raised (more than 3 x normal) serum levels of liver transaminase enzymes.
Calao 2006[54] (Italy)	Probably single centre, Uncontrolled before and after design	Acromegaly not responding to SSA. Serum IGF-1 at least 1.3 x the upper limit of the age-adjusted normal range. SSA washout 4 months	Treatment with DopA within 5 weeks of study start, hepatitis, drug abuse, pregnant or nursing women	16	Surgery: 87% Radiotherapy 12% SSA 100% DopA unclear	*Age: yrs* median 46, range 28-61 *Sex M/F* 47% / 53% *Duration of Acromegaly:* Unclear / not reported	Day 1 40 mg loading dose, then 10 mg / day titrated every 6 wks by 5 mg / day as necessary to normalise IGF-1 (max: 40 mg / day) Dose / day Mean 23.7 [SD 9.7] Median 25 Range 10 to 40	baseline vs after 12 months PEG	12 months	Base line. vs after 12 months PEG at dose required to normalise of IGF-1 Serum IGF-1 Serum GH Tumour size (MRI) Blood PEG levels Side effects / liver enzymes Signs and symptoms / ring size CVD markers (blood pressure; total chol; total chol /HDL-chol; TG; fibrinogen; glycosylated Hb; glucose; insulin ; HOMA)

Study / Reference Region / Country	Design of Study / Country	Population with acromegaly					Intervention *subcutaneously daily unless otherwise stated*	Comp.	F/up	Main Outcomes
		Inclusion Criteria	Exclusion Criteria	N	Previous Treatments (% by group)	Age / sex / other reported				
Pivonello 2007[57] (Italy) Mostly same patients as Calao 2006	Probably single centre, Uncontrolled before and after design	Acromegaly not responding to SSA. Serum IGF-1 at least 1.3 x the upper limit of the age-adjusted normal range. SSA washout 4 months Stable adenoma size for at least 12 months	Treatment with DopA within 5 weeks of study start. Hepatitis, drug abuse, pregnant or nursing women	17	Surgery: 82% Radiotherapy 12% SSA 100% DopA unclear	*Age: yrs* median 48 range 27-61 *Sex M/F* 47% / 53% *Duration of Acromegaly:* Unclear but> 6 months	Day 1 40 mg loading dose, then 10 mg / day titrated every 6 wks by 5 mg / day as necessary to normalise IGF-1 (max: 40 mg / day) Dose / day Mean 23.8 [SD 10.1] Median 25 Range 10 to 40	baseline vs after 6 and 18 months PEG	Maximum 18 months	Serum IGF-1 Serum GH PEG dose for normalisation of IGF-1
Schreiber 2007[58] (Germany)	Multi centre, "*Observational study*", uncontrolled before and after design 52 of 229 not evaluable	Not reported other than receiving PEG in Germany.	Not reported	229	Surgery: 90% Radiotherapy 43% 204 (89%) received but stopped SSA (octreotide); 139 uncontrolled IGF-1, 23 complications of treatment12 for both reasons.	*Age AT DIAGNOSIS: yrs* mean 40.5 SD 12.7 *Sex M/F* 47% / 53% *Duration of Acromegaly:* mean 9.1 years	Dose / day Mean 16.5 [SD 7.7] 94% patients Range 10 to 30	baseline vs 6, 12 , 24 months PEG	Maximum 24 months	Serum IGF-1 Adverse events (injection site reaction, elevated liver enzymes in serum, headache, increase in pituitary tumour volume.
Parkinson 2007[50] (Germany, Netherlands, Sweden, UK, and US) Many previous participants in Trainer 2000	Multi centre, retrospective uncontrolled before and after design 29 of 147 not evaluable	Diagnosis of acromegaly Serum IGF-1 at least 1.3 x the upper limit of the age-adjusted normal range SSA and DopA washout 2 and 5 weeks	Receiving LASSA.	147	Surgery: unclear / not reported Radiotherapy 58%% of 118 SSA unclear / not reported DopA unclear / not reported	*Age: yrs* median 44 range 20 - 78.7 *Sex M/F* 58% / 42% *Duration of Acromegaly:* mean 9.1 years	Day 1: an 80 mg loading dose, then from 10 mg / day titrated every 8 wks by 5 mg / day as necessary to provide IGF-1 normality. Mean dose duration 12 months [SD 7]	Dose PEG required to normalise IGF-1 correlation with Rx, sex, & baseline GH & IGF-1		

Appendix 4 Assessment of study quality

Quality assessment of the RCT was done according to recommendations in the Centre for Reviews and Dissemination handbook 2'nd edition.[45]

The following guidelines were used:

1. Randomisation

   A Method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigator could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

2. Double blinding

   A study must be regarded as double blind if the word 'double blind' is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos or dummies is mentioned and well described.

3. Withdrawals and dropouts

   Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points. An exception is made, if the presented data clearly describes that there have been no withdrawals.

Quality assessment of non-randomised and subgroup studies is summarised in the table below.

Table 15 Quality of non-randomised included studies

Study	Were eligibility criteria explicit?	Was sample source/selection described?	Were patients assembled at same time?	Was a method of diagnosis stated?‡	Were clinical details described?	Was individual patient data reported?	Was outcome assessment blinded?	Was blinding method adequately described?	Was follow up time stated?Φ	Were withdrawals stated?	Were reasons for withdrawal stated?
Barkan 2005	Y	N	CT	N	Y	N	N	NA	Y	Y	Y
Jorgensen 2005	Y	Y	CT	N	Y	N	N	NA	Y	Y	Y
Feenstra 2005	Y	N	CT	N	Y	N	N	NA	Y	N	NA
Van der Lely 2001[55]	Y	N	N	N	Y	N	N	NA	Y	Y	Y
Sesmilo 2002[47]	Y	N	CT	Y	Y	N	N	NA	Y	Y	Y
Fairfield 2002[48]	N	N	CT	N	Y	N	N	NA	Y	N	NA
Parkinson 2002[62]	N	N	CT	N	Y	Y†	N	NA	N	N	NA
Parkinson 2003a[53]	Y	N	CT	N	Y	N	N	NA	N	N	NA

[a] for a selection of patients. ‡ in most studies this was implicit ("patients with established diagnosis") rather than explicit. † in graphs. **Φ** where patient follow up varied but group value only provided N is entered

Study	Were eligibility criteria explicit?	Was sample source/selection described?	Were patients assembled at same time?	Was a method of diagnosis stated?‡	Were clinical details described?	Was individual patient data reported?	Was outcome assessment blinded?	Was blinding method adequately described?	Was follow up time stated?Φ	Were withdrawals stated?	Were reasons for withdrawals stated?
Parkinson 2003b[63]	N	N	CT	N	Y	Y†	N	NA	Y	N	NA
Parkinson 2004[52]	N	N	CT	N	N	Y†	N	NA	N		
Jehle 2005[56]	N	N	CT	N	Y	Y	N	NA	Y	Y	Y
Paisley 2006[51]	N	N	CT	N	Y	Y	N	NA	N	N	N
Biering 2006[49]	CT	Y	NA	N	N	Y[a]	N	NA	N	Y	Y
Colao 2006[54]	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	Y
Pivonello 2007[57]	Y	N	CT	Y	Y	Y	Y	Y	Y	Y	N
Schrieber 2007[58]	N	Y	N	N	Y	N	N	NA	Y	Y	N‡‡
Parkinson 2007[50]	Y	N	CT	N	Y	Y	Y	N	N	N	NA

‡ in most studies this was implicit ("patients with established diagnosis") rather than explicit ; **Φ** where patient follow up varied but group value only provided N is entered
‡‡ for adverse events only

Appendix 5 Results reported in included studies

In these tables the abbreviation PEG is often used for pegvisomant

Study	Outcomes (tumour /signs-symptoms)	Outcomes (GH, IGF-1, adverse events, safety, other)	Comments
Trainer 2000[46]	**Baseline tumor vol. (ml)** placebo: 1.9 ± 1.8 10 mg: 2.4 ± 2.6 1 15 mg: 3.3 ± 6 20 mg: 2.1 ± 1.9 **12-wk tumor vol. (ml)** placebo: 1.8 ± 1.8 10 mg: 2.4 ± 2.6 SS 15 mg: 3.4 ± 6.3 p=0.35 20 mg: 2.2 ± 2.0 p=0.91 **Change from base line in Ring size** placebo: –0.1 (2.3) 10 mg: –0.8 (1.6) 15 mg: –1.9 (2.0) 20 mg: –2.5 (3.3) **Change from base line in Total score** placebo: 1.3 (6.0) 10 mg: –2.5 (4.3) SS 15 mg: –4.4 (5.9) SS 20 mg: –4.7 (4.7) SS **Change from base line in Soft tissue swelling** placebo: 0.3 (2.3) 10 mg: –0.7 (1.6) 15 mg: –1.2 (2.3) 20 mg: –1.3 (1.3) SS **Change from base line in Arthralgia** placebo: 0.1 (1.8) 10 mg: –0.3 (1.8) 15 mg: –0.5 (2.5) 20 mg: –0.4 (2.1) **Change from base line in Headache** placebo: 0.1 (1.7) 10 mg: –0.4 (1.6) 15 mg: –0.3 (1.4) 20 mg: –0.3 (2.0) **Change from base line in Perspiration** placebo: 0.1 (1.7) 10 mg: –0.6 (1.6) 15 mg: –1.1 (1.3) SS 20 mg: –1.7 (1.6) SS **Change from base line in Fatigue** placebo: 0.7 (0.5) 10 mg: –0.5 (1.4) SS 15 mg: –1.3 (1.7) SS 20 mg: –1.0 (1.6) SS	**12-wk GH (ng/ml)** placebo: 7.6 ± 15.1 10 mg: 10.5 ± 11.8 15 mg: 21.4 ± 22.7 20 mg: 22.7 ± 27.8 **Change in GH (ng/ml)** placebo: –0.8 ± 5.0 10 mg: 2.7 ± 5.5 p= 0.08 15 mg: 9.2 ± 10.6 p=0.001 20 mg: 14.4 ± 21.2 p=0.001 **Adverse events that occurred in at least 10% of patients** **Upper respiratory tract infection** placebo: 5 (16) 10 mg: 5 (19) 15 mg: 4 (15) 20 mg: 5 (18) **Headache** placebo: 4 (12) 10 mg: 3 (12) 15 mg: 2 (8) 20 mg: 3 (11) **Injection-site reaction** placebo: 0 10 mg: 2 (8) 15 mg: 1 (4) 20 mg: 3 (11) **Pain** placebo: 2 (6) 10 mg: 2 (8) 15 mg: 1 (4) 20 mg: 4 (14) **Diarrhea** placebo: 1 (3) 10 mg: 1 (4) 15 mg: 0 20 mg: 4 (14) **Nausea** placebo: 1 (3) 10 mg: 0 15 mg: 2 (8) 20 mg: 4 (14) **Flatulence** placebo: 0 10 mg: 0 15 mg: 1 (4) 20 mg: 3 (11) **Baseline IGF-1(ng/ml)** placebo670 ± 288 10 mg: 627 ± 251 15 mg: 649 ± 293 20 mg: 732 ± 205 **12-wk IGF-1 (ng/ml)** placebo: 640 ± 288 10 mg: 449 ± 220 15 mg: 321 ± 203 20 mg: 279 ± 183 **(%) of Change from base line in serum IGF-1** placebo: –4.0 ± 16.8 10 mg: –26.7 ± 27.9 p=0.001 15 mg: –50.1 ± 26.7 p=0.001 20 mg: –62.5 ± 21.3 p=0.001 **Serum anti-GH antibodies:** placebo 10 mg 15 mg 20 mg were detected in 8 of the 80 pegvisomant patients (10%) in titers ranging from 1:4 to 1:64 (5 patients on pegvisomant 10 mg, 1 patient on 15 mg, and 2 patients on 20 mg). Liver enzymes except for the patient with the SAE, there were no significant increases in ALT or AST in any study group.	- Mean tumor volume did not change significantly in any patient, nor did tumor volume change significantly more in any pegvisomant group compared with placebo. - Frequency of adverse events was similar in the pegvisomant and placebo groups, except for injection site reactions - confidence intervals not reported; - short duration; - studied mixed population with no efficacy analysis by patient subgroups according to prior treatment exposure

Study	Outcomes (tumour /signs-symptoms, GH, IGF-1, adverse events, safety, other)	Comments
Van der Lely 2001[55]	**IGF-1, mean ± SD (mcg/l)** 6 months , N=131: 760 ± 306 12 months N=90: 806 ± 297 18 months N=39: 847 ± 321 **Baseline GH, mean ± SD (mcg/l)** 6 months, N=131: 10.9 ± 17.0 12 months N=90: 13.2 ± 19.7 18 months N=39: 19.2 ± 27.0 **Change in GH (ng/ml)** 6 months, N=131: 12.5 ± 2.1* 12 months N=90: 12.5 ± 3.1* 18 months N=39: 14.2 ± 5.7* **Tumor vol. (ml)** 6 months, N=131: 2.1 ± 2.5 12 months N=90: 2.4 ± 2.7 18 months N=39: 2.5 ± 2.6 **Adverse events occurred in 10% of patients:** Infection 52 (33) Headache 41 (26) Pain 36 (23) Influenza-like syndrome 33 (21) Accidental injury 28 (18) Diarrhea 23 (14) Hypercholesterolemia 23 (14) Back pain 21 (13) Asthenia 21 (13) Arthralgia 19 (12) Injection site reaction 18 (11) Sinusitis 16 (10) - Except for 9 cases (7 cases of pneumonia, a case of gluteal abscess, and a case of urosepsis), infections were generally nonserious, upper respiratory tract infections that rarely required treatment. -Injection site reactions occurred in 18 patients (11%) and were generally mild, erythematous, self-limiting, and did not require treatment. - Liver enzymes concentrations returned to normal within several months after stopping the drug. No clinically relevant changes were seen in vital signs, electrocardiograms, or chest radiographs. -Total serum cholesterol at baseline (mean ± SE: 5.23 mmol/l ± 0.08) was above the recommended concentration for therapeutic intervention (≥ 5.14 mmol/l) and remained relatively stable during pegvisomant treatment (5.18 mmol/l ± 0.11). Of 23 patients who were reported to have hypercholesterolemia as an adverse event, 18 had total cholesterol greater than 5.14 mmol/l at baseline.	- long-term evaluation of up to 18 months; assessed anti-pegvisomant antibodies. - Uncontrolled study prevents conclusions about the potential for certain adverse events to develop on pegvisomant, such as infections; durability of response was based on only 38 patients; results may not reflect longer-term use of pegvisomant - The initial study was an RCT of 112 participants, the extension was 167.Therfore new patients added in a non RCT design. Normal IGF-1 was achieved in 80 (97%) of 90 patients treated for 12 months or more. In 11 patients, IGF-1 decreased to below age-adjusted normal limits and 9 of these patients required a decrease in dose.

Study	Outcomes	Comments
Fairfeild 2002[48]	**Serum markers of bone turnover** Osteoclacin *-2.2±0.44 vs placebo +0.01± 0.39 nmol/L* P=0.009 favours Pegvisomant NTx *-4.4±1.4 vs placebo +1.0±nM* P=0.024 favours Pegvisomant PICP -23.6±*9.6 vs placebo +18.1±12.8 mcg/L* P=0.002 favours Pegvisomant	Markers of both bone formation and resorption rapidly reduced when IGF-I is normalized. These are surrogate outcomes and there is a need for good correlating studies and clinically important outcomes
Sesmilo 2002[47]	**Change from base line at 3 months for the prospective placebo** Total Cholesterol HLD LDL Total/HDL Triglyceride CRP* P=0.10 IL-6 Lipoproien Homosysteine GH* P=0.001 Glucose Insulin IRHOMA IGF-I* P=0.0001 **The longitudinal open label study control study** **Change from base line** Total Cholesterol P=0.05 HLD LDL Total/HDL Triglyceride P=0.007 CRP P=0.0002 IL-6 Lipoproien Homosysteine GH P=0.0001 Glucose Insuline IRHOMA IGF P=0.0001	These are surrogate outcomes and there is a need for good correlating studies and clinically important outcomes
Parkinson 2003 a[53]	**Changes in markers of bone turnover and soft tissue formation following PEG treatment after induced serum IGF-I normalization in 16 patients** IGF-I 699±76 at baseline vs 242±28 during treatment, p <0.0001 in favour of pegvisomant PIIINP 4.3±0.3 at baseline vs 3.1±0.3 p<0.01 in favour of pegvisomant OC 47(14-109) at baseline vs 21(10-73) p<0.001 in favour of pegvisomant CTx 0.8(0.2-2.4) at baseline vs 0.4(0.03-1.3) p<0.0001 in favour of pegvisomant PINP 70±12 at baseline vs 38±8 p<0.01 in favour of pegvisomant BAP 147±29 at baseline vs 120 ±23 p<0.05 in favour of pegvisomant Tx/Cr ratio 92±27 at baseline vs 56±14 p<0.01 in favour of pegvisomant	
Parkinson 2003 b[63]	**Pegvisomant induced serum IGF-I was associated with:** A rise in fasting leptin 8.9 (1.62-58.3) vs on peg 12.7(2.3-90.8) p<0.0001 Fasting insulin 9.9(7.2-36.7) vs on peg 8.3(4.7-20.8) p>0.05 Insulin resistance3.97±2.8 vs on peg 2.28±1.3 p<0.05	Serum leptin correlates positively with fat mass.

Study	Outcomes	Comments
Feenstra 2005[59]	**IGF concentration** 18/19 (95%) patients had normal IGF-I concentration at 42 weeks (at least 50 mg pegvisomant per week) in combined therapy. 24.4nmol/L± SD12.0 **No signs of pituitary growth were seen on MRI in the 19 patients at 6 months treatment** **Cost:** "The combination therapy could save £40,300 per year for patients who need 40 mgof daily pegvisomant monotherapy**"**	Mild non progressive increase in liver enzymes were observed in 10 (38%) patients . Increased compliance in weekly pegvisomant.
Jorgensen 2005[60]	**IGF-1 total serum levels** decreased with co-treatment significantly compared to SMS458±67 SMS, 376±51 (10 mg), 269 (15) mg, 195±24 Combined p<0.0001 **Free and bioactive IGF-1** changed in a similar pattern. **GH levels** 5.1±1.3 SMS but Increased GH 14.6±4.9 (10 mg), 19.7±6.5 (15mg), 11.8±2.8 combined p<0.01 **Plasma glucose levels (2-h oral glucose tolerance test)** 10.3±0.7 SMS, 7.2±0.7 (10 mg), 6.5±0.5 (15mg), 8.0±0.8 combined p=0.02	
Barkan 2005[64]	**Effects on glucose homeostasis: at 32 weeks** With DM: fasting plasma glucose 5.0(4.0-6.2) p≤0.003 vs 4 weeks Without DM: fasting plasma glucose 4.6(4.4-5.1) p≤0.0001 vs 4 weeks **Effect on IGF-I and GH concentrations** Pegvisomant reduced IGF-I concentration to the age adjusted normal range in 78% Of patients by 32 weeks. (38 of 49 patients). GH increased from 3 mcg/litre at 4 weeks to 17 mcg/litre at 24 weeks **Tumour volume** No significant change in the study period of 32 weeks compared with the start. (median change ,0.02cm^3 range [-0.73 to 1.1; p=0.3) **Safety parameters** Three out of 53 patients had alanine aminotransferase at week 20 greater than 3.5 times At week 0 19/49 (40%) had sign of gallbladder disease, 15 with gallstones, 4 had sludge. At 32 weeks 13 patients gallstones and 3 with sludge.	Not stated if the cases of gallstones were newly developed at the last follow up

Appendix 6 Results for Tumour volume

Trainer (2000) RCT

Table 16 Group mean tumour volumes (95% CI) reported in Trainer (2000)

treatment duration	placebo (*n = 31)*			10 mg / day *(n = 26)*			15 mg / day (*n = 26)*			20 mg / day (*n = 28)*		
	mean ml	*LCI*	*UCI*	mean ml	*LCI*	*UCI*	mean ml	*LCI*	*UCI*	mean ml	*LCI*	*UCI*
0	1.9	1.2	2.6	2.4	1.3	3.5	3.3	0.8	5.8	2.1	1.4	2.8
12 weeks	1.8	1.1	2.5	2.4	1.3	3.5	3.4	0.9	5.9	2.2	1.4	3.0

van der Lely (2001)

In the study of van der Lely (2001) 131 of a possible 160 MRI image pairs were collected, one image at baseline and another at an average of 11.5 months into pegvisomant treatment. No statistically significant change from baseline was observed. At baseline group mean tumour volume was 2.41 ml (95% CI; 1.8 to 3.0) and after treatment was 2.37 ml (95% CI; 1.8 to 3.0). The mean of individual change from baseline was – 0.033 ml (95% CI; – 0.15 to +0.08; p = 0.353 for difference from zero change). Two patients had progressive tumour growth that required treatment, the authors could attribute no cause, and there was no relationship between duration of treatment and change in tumour size.

Small studies

Colao reported results for 14 patients.[54] At baseline group mean tumour size was 1.23 ml (95% CI; 0.55 to 1.91); after treatment mean volume was 1.20 ml (95% CI; 0.46 to 1.95); the mean change in volume was – 0.026 ml (95% CI; – 0.21 to + 1.56).

The dual-therapy (pegvisomant + SSA) studies of Feenstra[59] and Jorgensen[60] reported similar clinically and statistically non-significant results. In the study of Jehle,[56] which explored decreased dose frequency, 2 patients (of 10) showed small clinically insignificant increases in tumour size (duration of treatment 12 to 20 weeks).

Appendix 7 Changes in IGF-1 levels

Trainer (2000) RCT

Table 17 Serum IGF-1 levels reported by Trainer 2000

Duration of treatment	**placebo** n = 31			**10 mg / day** n = 26			**15 mg / day** n = 26			**20 mg / day** n = 28		
	IGF-1 ng / ml	*LCI*	*UCI*	IGF-1 ng / ml	*LCI*	*UCI*	IGF-1 ng / ml	*LCI*	*UCI*	IGF-1 ng / ml	*LCI*	*UCI*
0 weeks	670.0	*564.4*	*775.6*	627.0	*525.6*	*728.4*	649.0	*528.1*	*769.9*	732.0	*732.0*	*811.5*
3 weeks	688.5	*562.8*	*814.1*	442.3	*363.1*	*521.5*	373.1	*285.8*	*460.4*	361.5	*361.5*	*448.4*
6 weeks	669.2	*567.1*	*771.3*	415.4	*328.2*	*502.5*	342.3	*255.0*	*429.6*	269.2	*269.2*	*340.3*
9 weeks	653.8	*551.7*	*755.9*	438.5	*335.5*	*541.5*	292.3	*212.9*	*371.7*	280.8	*280.8*	*351.8*
12 weeks	640.0	*534.4*	*745.6*	449.0	*360.1*	*537.9*	321.0	*237.2*	*404.8*	279.0	*279.0*	*350.0*

van der Lely (2001)

Many participants from the Trainer RCT entered the non-randomised uncontrolled extension study of van der Lely 2001.[55] Pegvisomant dose was titrated so as to achieve normal range IGF-1 with a maximum allowed dose of 40 mg / day. The total number of patients was 160, and IGF-1 data was reported for varying numbers in groups that accumulated treatment periods of 6, 12 or 18 months.
Results are given below.

Table 18 Serum IGF-1 levels reported by van der Lely

Duration of treatment	**6 month group n = 131**			**12 month group N = 90**			**18 month group n = 39**		
	IGF-1 ng / ml	***LCI***	***UCI***	**IGF-1 ng / ml**	***LCI***	***UCI***	**IGF-1 ng / ml**	***LCI***	***UCI***
0 months	760.0	*707.1*	*812.9*	806.0	*743.8*	*868.2*	847.0	*743.0*	*951.0*
6 months	358.2	*309.1*	*407.3*	390.1	*347.8*	*432.3*	390.1	*325.5*	*454.7*
12 months				290.8	*248.5*	*333.1*	315.6	*251.0*	*380.2*
18 months							326.2	*268.8*	*383.7*

Schrieber (2007)

Out of a recruited population of 229 Schreiber collected IGF-1 data for 157 patients at baseline and for 147, 102, and 39 patients after 6, 12 and 24 months.[58] At baseline 11% had normal range IGF-1 and at 6, 12 and 24 months of treatment 64%, 71%, and 76% were in normal range.

Small studies

Colao recruited 16 patients whose IGF-1 was not normalised despite SSA treatment.[54] After washout of SSAs mean baseline IGF-1 ranged from 525 to 1023 ng / ml (mean 789; 95% CI 715 to 862). One patient failed to inject pegvisomant. All 15 patients that injected showed substantial reductions in IGF-1 level during treatment. Two were withdrawn after 6 months, one because of rise in serum transaminase enzyme levels and the other through inability to follow the protocol. After 9 months another patient withdrew because of poor compliance. Of 14 patients evaluated 8 (57%) reduced IGF-1 to within normal range and 3 more to within 1 to 1.3 times normal range.

Feenstra 2005,[59] Jorgensen 2005[60] and Jehle 2005[56] all modified the usual dose regimen of daily pegvisomant; the former two studies combined pegvisomant with SSA therapy, whilst Jehle attempted reduction of dose frequency. Because daily pegvisomant is very expensive these strategies might have reduced the overall cost of maintaining IGF-1 within normal range at least for some patients.

Feenstra studied 26 patients who had been treated for at least 6 months with long acting SSA but remained with IGF-1 levels above their normal range.[59] Patients were continued with monthly 30 mg long acting octreotide or 120 mg lanreotide autogel supplemented with weekly (not daily) pegvisomant started at 25 mg and titrated dose to achieve normal range IGF-1 (maximum permissible dose: 80 mg / week pegvisomant). At 18 weeks IGF-1 was normalised in 21/26 (81%) patients, and at 42 weeks in 95% (18/19 evaluated) the median weekly pegvisomant dose to achieve normalisation in those normalised was 60 mg / week.

Jorgensen also examined combined pegvisomant and SSA therapy in patients failing to normalise on SSA alone.[60] The design of the study is illustrated below. Five study phases consisted of: therapy with SSA, withdrawal from SSA for 2 months (termed disease “active” phase), pegvisomant at 10 mg / day (6 weeks), pegvisomant at 15 mg / day (6 weeks), and finally 12 weeks of 15 mg / day pegvisomant plus 30 mg long acting SSA every 2 to 4 weeks. Serum IGF-1 levels

were measured at the end of each phase of the study; results are shown in Figure 18.

Table 19 Study design for Jorgensen 2005.

N=10	N=11[§]	N=11	N=11	N=10[§§]
Long acting SSA (30 mg IM every 2 to 4 weeks)	2 months SSA withdrawal	6 weeks PEG 10 mg /day	6 weeks PEG 15 mg /day	12 weeks PEG 15 mg /day + long acting SSA (30 mg every 4 weeks or every 2 to 4 weeks)
[§] A further (eleventh) patient joined at this study phase having withdrawn from SSA before start of study. [§§] One patient withdrawn at this last stage because of raised liver enzyme levels in serum. Peg: pegvisomant				

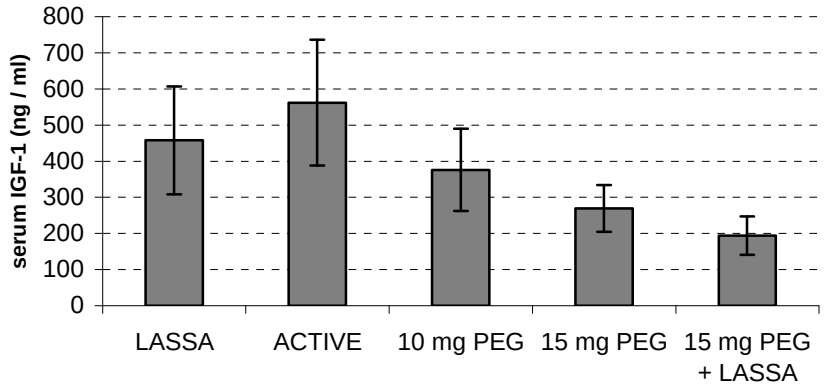

Figure 18 IGF-1 levels (and 95% CI) at end of study phases in Jorgensen 2005

Combined therapy lowered IGF-1 levels more effectively than single therapy with either LASSA or pegvisomant at 10 or 15 mg / day. The difference between 15 mg / day pegvisomant and combined treatment just failed to reach statistical significance at the 5% level. On combined therapy all but one patient achieved normal IGF-1 levels (unclear if this was calculated ITT). Data about normality for the monotherapy at 15 pegvisomant mg / day was not reported so the benefit of combination in terms of IGF-1 normalisation was unclear. Jorgensen also reported serum levels of "bio-active" IGF-1.[60] The results were very similar to those for total serum IGF-1.

Jehle 2005 administered pegvisomant to 10 patients who had failed to normalise IGF-1 with DopA or with SSAs.[56] Mean treatment duration was 15.3 months; all patients normalised IGF-1 and 5 of these were able to reduce frequency of dose administration to less than daily while retaining normal IGF-1.

IGF-1 levels were also reported in studies by Parkinson 2002,[62] 2003a,[53] 2003b,[63] 2004,[52] 2007,[50] Sesmilo 2002,[47] Fairfield 2002,[48] Paisley 2006,[51] and Barkan 2005.[64] and are not considered further here because thay likely represent double counting of data for patients reported in Trainer 2000,[46] and or van der Lely 2001.[55]

Appendix 8 Changes in GH levels

Trainer (2000)

Table 20 GH levels at baseline and after 12 weeks PEG treatment (Trainer 2000)

treatment duration	placebo (*n = 31*)			10 mg / day (*n = 26*)			15 mg / day (*n = 26*)			20 mg / day (*n = 28*)		
	mean ng / ml	*LCI*	*UCI*	mean ng / ml	*LCI*	*UCI*	mean ng / ml	*LCI*	*UCI*	mean ng / ml	*LCI*	*UCI*
0	8.7	1.3	16.1	7.8	3.6	12.0	11.5	2.2	20.8	8.1	4.0	12.2
12 weeks	7.6	2.1	13.1	10.5	5.7	15.3	21.4	12.2	30.6	22.7	11.9	33.5

van der Lely (2001)

Table 21 GH levels reported in extension study of van der Lely

trearment duration	6 month group (*n = 131*)			12 month group (*n = 90*)			18 month group (*n = 39*)		
	mean ng / ml	*LCI*	*UCI*	mean ng / ml	*LCI*	*UCI*	mean ng / ml	*LCI*	*UCI*
0	10.9	13.8	8.0	13.2	9.1	17.3	19.2	28.0	10.4
6 months	22.3	27.3	17.4	26.1	15.1	37.0	32.3	46.6	17.9
12 months				25.5	14.3	36.8	32.3	49.5	15.0
18 months							32.1	49.0	15.2

It is not possible to determine from this data whether, on average, continued treatment beyond 12 weeks induces further rise in GH because baseline levels varied considerably between groups and patient withdrawals or lack of follow up may bias the data.

Small studies

Colao reported individual GH levels for 16 patients that fitted the licensed indication for pegvisomant.[54] After washout of SSAs the mean baseline GH ranged from 3.4 to 74.8 ng / ml (mean 23 ng / ml; 95% CI 10.9 to 35.0). After treatment, discounting one patient who failed to inject pegvisomant, the range was 6.3 to 145 ng / ml (mean 33.1; 95% CI 11.3 to 54.9). Not all patients increased their GH level. The range of change from baseline was –17 to + 52 ng / ml and group mean change from baseline was +10.8 ng / ml (95% CI –1.7 to +23.3).

Jorgensen 2005 performed a study with five phases (see Table 19) in 11 patients that had failed to normalise IGF-1 when treated with SSA alone.[60] GH levels measured at the end of each phase of study are summarised in Figure 19.

Pegvisomant treatment more than doubled group mean GF levels. Supplementing 15 mg daily pegvisomant with long acting SSA combined therapy (every 2 to 4 weeks) apparently suppresses some of the induced rise due to pegvisomant; this difference of group means does not reach statistical significance at p 0.05 level.

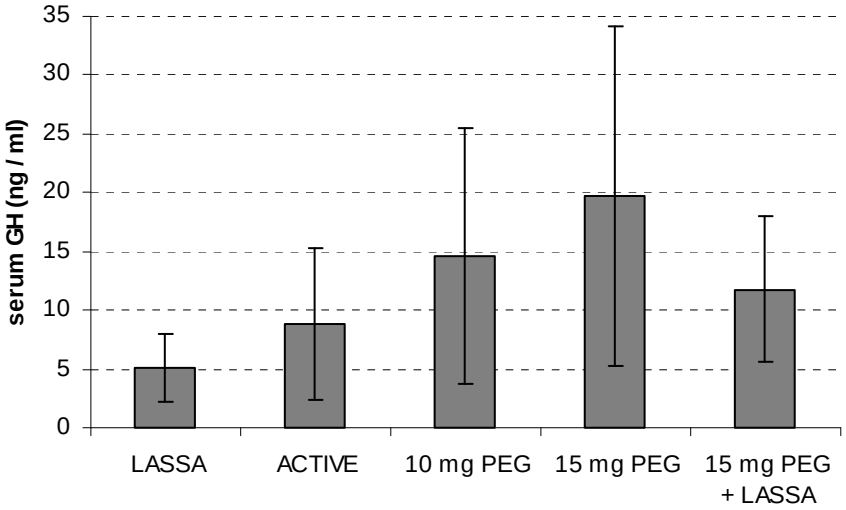

Figure 19 Serum GH levels at the end of each study phase reported by Jorgensen (2005)

Sesmilo 2002 also reported on GH, but these data likely double count results encompassed within the Trainer and van der Lely studies.[47]

Appendix 9 Adverse events reported in non randomised studies

Table 22 Rate of adverse events reported in studies of pegvisomant treatment

	Non-randomised studies (pegvisomant dose adjusted to normalise IGF-1 level).			
Adverse event	van der Lely (2001) ¶ n = 160	Scheiber (2007) ¶¶ n = 229	Jehle (2005) n = 10	
Infection	52 (33%)		1 (10%)	
Headache	41 (26%)	4 (1.7%)	3 (30%)	
Injection-site reaction	18 (11%)	17 (7.4%)		
Pain	36 (23%)			
Diarrhoea	23 (14%)			
Influenza-like syndrome	33 (21%)			
Accidental injury	28 (18%)			
Hypercholesterolemia	23 (14%)			
Back pain	21 (13%)			
Asthenia	21 (13%)			
Arthralgia	19 (12%)			
Sinusitis	16 (10%)			
Insomnia (transient)			2 (20%)	
Fatigue			3 (30%)	

¶ Number of patients (%) with adverse events that occurred in at least 10% of patients. ¶¶ Number of patients (%) with adverse events occurring in > 1% and judged potentially causally related to pegvisomant treatment.

Appendix 10 Further outcomes reported in subgroup or non-randomised studies

Cardiovascular risk

There were small numbers of participants in these studies. Changes for most markers analysed were not statistically significant (Table 23). The results for standard risk markers were not always consistent across studies. Thus total cholesterol change was statistically insignificant in two studies but significantly increased in two others.[51,62] In one study a significant increase in LDL cholesterol was observed but not of HDL cholesterol, whereas in another there was a statistically significant increase in HDL cholesterol but not LDL cholesterol. One study[47] reported a statistically significant fall in TG while three others[51,54,62] found no significant change. Two studies reported a fall in lipoprotein *a* levels.[47,62]

Table 23 Pegvisomant treatment induced changes in risk indicators for cardiovascular disease

	Sesmilo 2002[47] § n = 26		**Colao 2006[54] n = 16**	**Parkinson 2002[62]† n = 20**	**Paisley 2006[51]†† n = 20**	
PARAMETER	Mean change from baseline	*P*	Paired t test Before v. after Tx *P*	Paired t test Before v. after Tx *P*	Cases: Before Tx v. after Tx *P*	Cases before Tx v. Healthy controls *P*
Total chol (mM)	0.22	*NS*	*NS*	***INC <0.01***	***INC <0.01***	*0.16*
HDL chol (mM)	0.006	*NS*	***INC 0.0017***	*NS*	—	—
LDL chol (mM)	-0.13	*NS*	—	***INC <0.01***	—	—
[Total/HDL] chol	0.21	*NS*	***RED 0.0012***	—	—	—
TG (mM)	0.25	***0.007***	*NS*	*NS*	*0.3*	*0.13*
Lipo*(a)* (mg/l)	-70	***0.039***	—	***RED <0.01***	—	—
Apo B	—	—	—	***INC <0.01***	—	—
Apo A1	—	—	—	***INC <0.05***	—	—
Homocysteine (μM)	-0.16	*NS*	—	—	—	—
CRP	2	***0.0002***	—	—	—	—
Interleucin 6	0.17	*NS*	—	—	—	—
Blood pressure	—	—	*NS*	—	—	—
Fibrinogen	—	—	*NS*	—	—	—
Heart rate	—	—	*NS*	—	—	—
MMP-2 (ng / ml)	—	—	—	—	***RED <0.001***	***HIGHER <0.001***
MMP-9	—	—	—	—	*0.76*	*0.87*
VEGF	—	—	—	—	***RED 0.008***	*0.18*

§ results for the open label part of the study, patients included if they normalised IGF-1 with treatment. It is unclear if the number of patients analysed was 34 or 26. † Units for Total chol and total TG given in paper as mM but are actually mg/dl. †† It is possible that some participants may have been used in both these studies. Apo A1 = apoprotein A1 (on HDL & chylomicrons). Apo B = apoprotein B (on LDL). chol = cholesterol CRP = C-reactive protein. HDL = high density lipoprotein. ***INC =*** increased. LDL = low density lipoprotein. Lipo *(a)* = lipoprotein little a. MMP = matrix metalloproteinase. *NS*= not statistically significant. *P* = probability. PEG = pegvisomant ***RED*** = reduced. TG = triacyl glyceride. Tx = treatment. VEGF = vascular endothelial growth factor.

Cardiac structure and function

Increased prevalence of cardiac problems is thought to lead to increased mortality in acromegaly.[3]

Pivonello used Doppler echocardiography to study the effect of pegvisomant in 17 patients whose IGF-1 had not normalised with other pharmacotherapy.[57] All but three participants were the same as those that took part in the study of Colao.[54] Cardiac function was monitored at 6 month intervals to 18 months. Five patients dropped out before end of follow up. At 18 months the 12 completing patients exhibited statistically significant changes from base line in the following measures: left ventricular mass; left ventricular mass index; left ventricular posterior wall thickness; interventricular septum thickness; left ventricular ejection fraction; isovolumic relaxation time; early to late ratio of atrial peak velocities. Ten of the twelve had normalised IGF-1 by 18 months. A significant correlation (P 0.001) was reported between change from baseline in ejection fraction and change from baseline in IGF-1. The results imply that pegvisomant treatment may improve cardiac structure and function.

Indicators of bone turnover

Two studies, Parkinson 2003a[53] and Fairfield 2002,[48] presented data on serum markers of bone metabolism. The participants in Fairfield (n=27) were a subgroup from the RCT of Trainer; measurements were made at baseline and at 12 weeks and statistical tests compared change from baseline in the placebo group (n=7) versus the pegvisomant group (n=20). The participants in Parkinson (n=16) were also some of the patients who had started pegvisomant or placebo in the Trainer RCT and who then entered the open label pegvisomant extension of van Lely; measures were made at baseline and at the first occasion normal IGF-1 was observed (all 16 achieved normalisation) and statistical tests compared baseline value versus value at normalisation.

Bone formation was monitored by measuring osteocalcin, amino- or carboxy-terminal propeptides of Type I procollagen, and bone alkaline phosphatase activity (Parkinson only). Bone resorption was monitored by measuring amino- or carboxy-

terminal cross linked telopeptides of Type I collagen, and (Parkinson only) urinary ratio of amino terminal cross linked telopeptides of Type I collagen : creatinine. In addition Parkinson measured serum amino-terminal propeptide of Type III procollagen as a marker for soft tissue formation.[53]

The results are summarised in Table 24. They support the proposition that pegvisomant reduces bone turnover in acromegaly patients; how this translates to patient benefit requires further investigation.

Table 24 Effect of pegvisomant on markers of bone turnover and soft tissue formation

	Parkinson 2003[53] Φ			Fairfield 2002[48] ΦΦ		
MARKER	baseline	at IGF-1 normalis'n	P	placebo 12 wks	pegvisomant 12 wks	P
Bone formation						
osteocalcin	47$^{\theta}$ (14 – 109)	21 (10 - 73)	< 0.001	+0.01$^{\theta\theta}$ (0.39)	-2.2 (0.44)	0.009
terminal propeptide procollagen I	70$^{\theta}$ (12)	38 (8)	< 0.01	+18.1$^{\theta}$ (12.8)	-23.6 (9.6)	0.022
bone alkaline phosphatase	147$^{\theta\theta\theta}$ (29)	120 (23)	< 0.05			
Bone resorption						
cross linked telopeptide of collagen I	0.8$^{\Psi}$ (0.2 – 2.4)	0.4 (.03 – 1.3)	<0.0001	+1$^{\theta\theta}$ (0.3)	-4.4 (1.4)	0.024
urinary ratio cross linked telopeptide : creatinine	92$^{\theta\theta\theta}$ (27)	56 (14)	< 0.01			
Soft tissue formation						
terminal propeptide of procollagen III	4.3$^{\theta}$ (0.3)	3.1 (0.3)	<0.01			

Φ data are mean (SEM) or median (range); ΦΦ data are mean (SEM); θ ug/L; θθ nmol/L; θθθ units unclear. Ψ pmol/L.

Indicators of metabolic improvement

GH and IGF-1 have manifold metabolic effects particularly counteracting or modulating the roles of insulin in glucose and lipid metabolism.[3] Acromegaly is associated with metabolic disturbance including impaired glucose tolerance and overt diabetes.[3]

Several non-randomised studies reported the effect of pegvisomant on laboratory measures relating to insulin and or glucose metabolism; studies included those of Barkan 2005 (n=53),[64] Parkinson 2002 (n=20),[62] Parkinson 2003b (n=16),[63] Colao 2006 (n=16),[54] Jehle 2005 (n=10),[56] Jorgensen 2005 (n=11),[60] Measures reported included fasting glucose, oral glucose tolerance test, glycated-haemoglobin levels, fasting insulin, and leptin levels. Most studies examined change from baseline. The

general direction of findings was for a favourable change indicative of improved metabolic adjustment.

Appendix 11 Modelling appendix

Since life tables were the source of data we used the Gompertz distribution to fit curves to data.

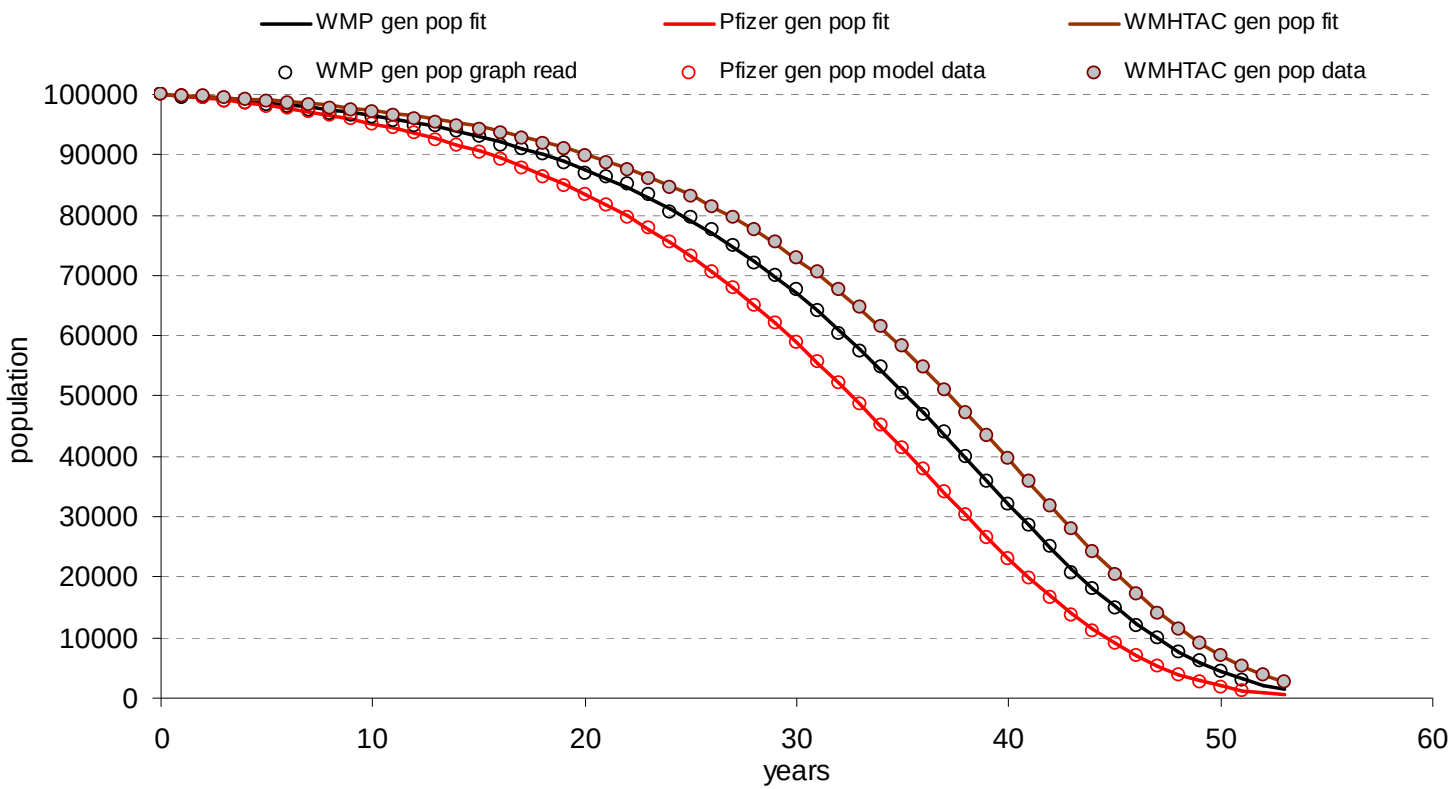

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Figure 20 Gompertz fits to three general population survival profiles used in economic modelling of PEG treatment

Figure 20 shows Gompertz fits to the survival data for the general populations used in the MM WMP and WMTAC models. As can be seen the fits are good. Similar good fit was observed for the MM treatment and standard care data Figure 21.

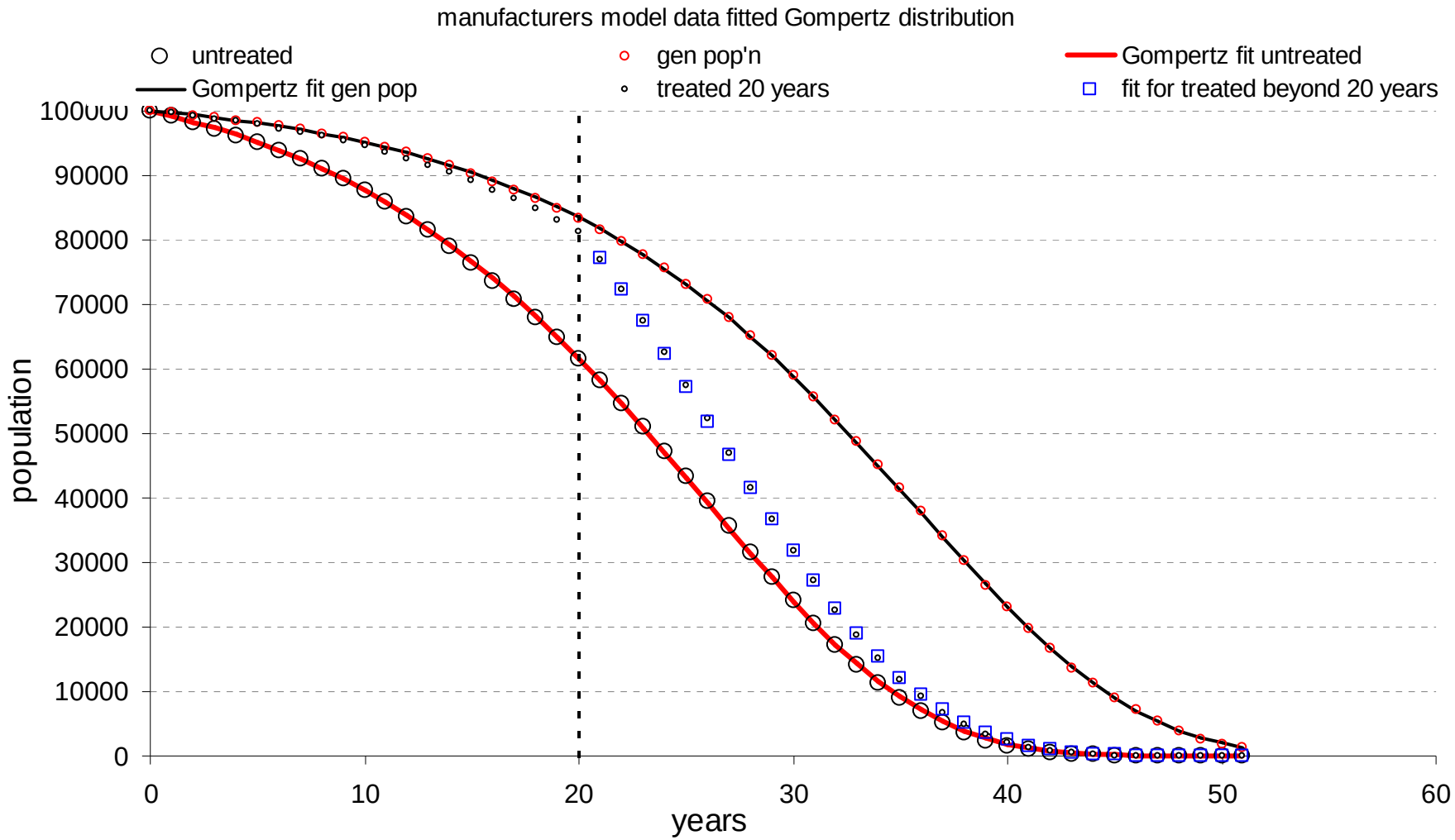

Figure 21 Gompertz fit to MM data.

To explore the effect of different choices of SMR on the derived survival profile for the SC population we applied the Gompertz distribution (Figure 22) $P = e^{(\lambda/S\gamma)(1-e^{\gamma t})}$ Where P = proportion surviving; λ & γ = constants; S = SMR

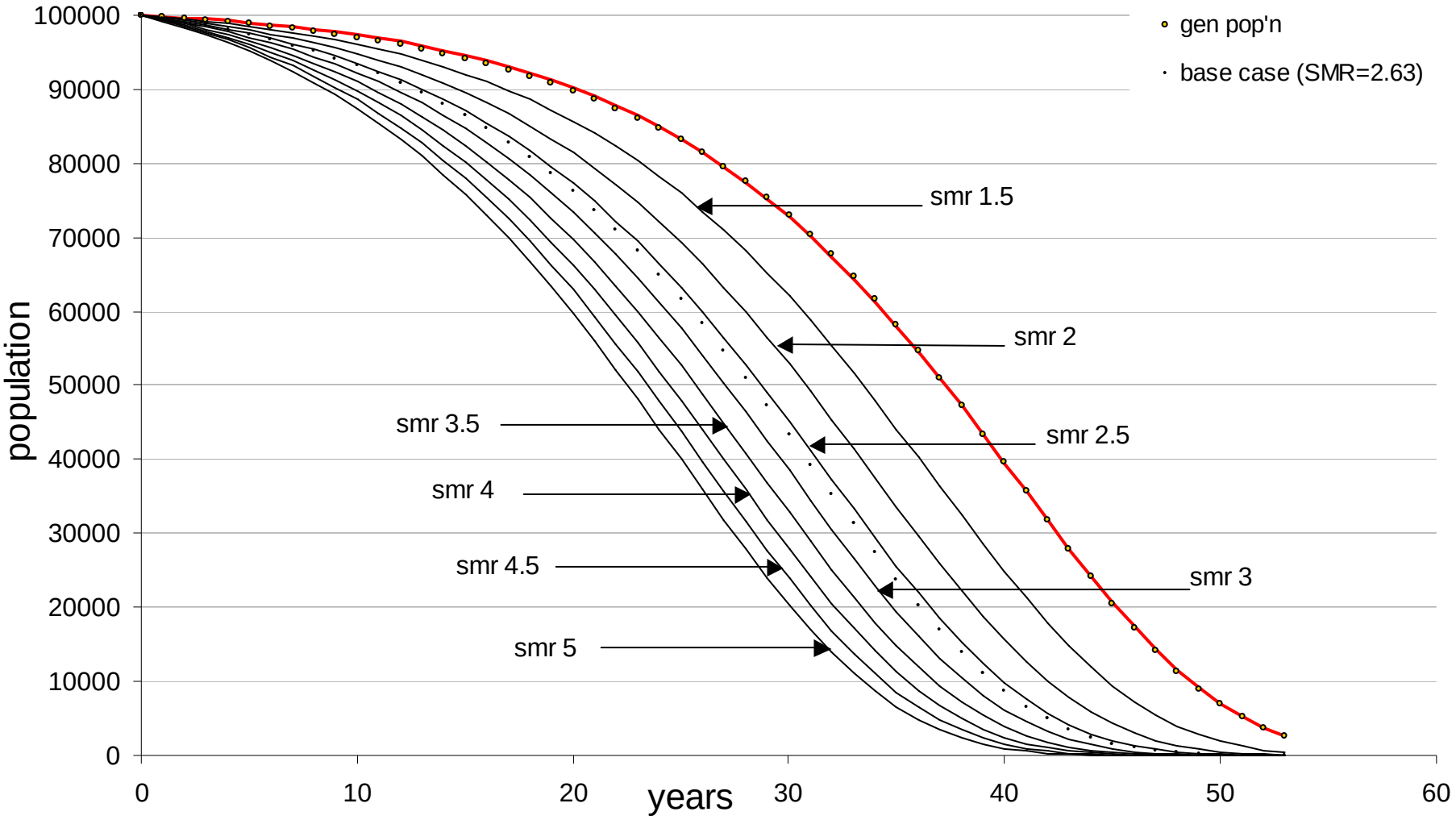

Figure 22 Effect of increasing SMR (1.5 to 5.0) on the survival profile of the standard care population

Appendix 12 Drug costs

Table 25 Drug costs for standard care package

ITEM	UNIT COST (£)	NO UNITS / INJECTION OR / DOSE	NUMBER INJECTIONS OR DOSES / YEAR	PROPORTION PATIENTS	ANNUAL COST	SUBTOTAL	SOURCE
Somatuline autogel (60 mg)	525	1	13	0.125	853.12		BNF 2007[42]
Sandstatin LAR (30 mg)	1062.5	1	13	0.125	1726.56		BNF 2007[42]
Somatuline autogel (120 mg)	902	1	13	0.125	1465.75		BNF 2007[42]
Sandostatin LAR (2 x 30 mg)	2125	1	13	0.125	3453.13		BNF 2007[42]
Cabergoline Distinex tablet (0.5 mg)	3.755	0.5	365	0.25	171.32		BNF 2007[42]
						7669.88	
Staff nurse / min	0.483	5	13	0.5	15.71		Curtis & Netten[74]
Outpatient appointment	78.25	1	13	0.5	508.63		Curtis & Netten[74]
						524.33	
TOTAL						**8194.23**	

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