Scottish Medicines Consortium

pegvisomant 10mg, 15mg, 20mg powder and solvent for injection (Somavert®) No. (158/05)

Pfizer Ltd.

4 March 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Pegvisomant (Somavert®) is not recommended for use within NHS Scotland 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. Pegvisomant reduces IGF-1 levels significantly, as well as improving some of the clinical manifestations of acromegaly. Although it is acknowledged that this is an orphan drug the cost-effectiveness is poor.

The licence holder has indicated their decision to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Pegvisomant 10mg, 15mg, 20mg powder and solvent for injection

Licensed indication under review

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 insulin-like growth factor 1 (IGF-1) concentrations or was not tolerated.

Dosing information under review

Loading dose: pegvisomant 80mg as a subcutaneous injection, under medical supervision.
Thereafter: pegvisomant 10mg once daily as a subcutaneous injection. Dose adjustments can be made in 5mg/day increments, maintaining serum IGF-1 levels (measured every 4-6 weeks) within the age adjusted normal range and to maintain an optimal therapeutic response. Maximum dose: 30mg per day.

UK launch date

10 May 2004

Comparator medications

none

Cost per treatment period and relevant comparators

Drug	Dose	Cost per day (£)*	Cost per year (£)*
Pegvisomant	**10-30mg once daily, as a subcutaneous injection**	**50 - 150**	**18 250 – 54 750**

* British National Formulary 48th edition (September 2004)

Pfizer currently provides a home delivery service and provides the loading dose and first month of pegvisomant free of charge. This has not been included in the above costs.

Summary of evidence on comparative efficacy

Two studies investigating pegvisomant have been conducted in patients with acromegaly. The first study was a 12 week randomised double blind placebo controlled study in 112 patients with a diagnosis of acromegaly, based on symptoms and signs at presentation, and a serum IGF-1 concentration at the second screening of at least 1.3 times the upper limit of the age-adjusted normal range, according to local laboratory values. Patients were excluded if they had received a long-acting somatostatin analogue within 12 weeks before enrolment. Patients were stratified according to the serum IGF-1 concentration at the second screening visit (1.3-2.0 times or > 2.0 times the upper limit of the age adjusted normal range) and then randomly assigned to receive either pegvisomant (10mg, 15mg or 20mg subcutaneous injection once daily) or placebo. A loading dose of pegvisomant 80mg subcutaneous injection or matching placebo was given to all patients. The primary efficacy endpoint was the percentage change in serum IGF-1 concentration from baseline to end of study. Secondary endpoints included incidence of normalisation of IGF-1, reduction in acid labile subunits and free IGF-1, IGF binding protein 3 (IGFBP-3), Growth Hormone (GH), acromegaly signs and symptoms (using a questionnaire, measured on scales of 0-8 for each of soft-tissue swelling,

arthralgia, headache, perspiration and fatigue, giving a range of 0-40 for the overall score) and ring size of the non-dominant hand ring finger (standard European jeweller's rings). The number of patients in the placebo, pegvisomant 10mg, 15mg and 20mg groups were 31, 26, 26, and 28, respectively.

The second study was a long-term open label study of patients with acromegaly who had previously received pegvisomant according to one of two protocols; the previously described protocol and a second protocol in which 38 patients received weekly dosing before being switched to a daily dosing protocol. Data from daily dosing only were included in the efficacy analysis. Eligibility criteria were as described in the first study. The daily dosing in both protocols began at 10mg per day and was titrated as necessary in increments of 5mg per day until the patients IGF-1 concentration was normal or a maximum dose of 40mg per day was reached. Patients were placed in cohorts on the basis of whether they had completed at least 6, 12, or 18 months on continuous daily pegvisomant treatment at the time of data cut-off. The cohorts were cumulative; therefore for example, all patients in the 18 month treatment cohort were included in the 6 and 12 month cohorts. A primary outcome for the trial was not stated, however treatment efficacy was assessed by measuring changes in tumour volume by magnetic resonance imaging (MRI), and serum GH and IGF-1 concentrations. 152 patients were included in the efficacy analysis with 131, 90 and 39 patients in the 6, 12, and 18 month cohorts.

Primary endpoints

In the first study, the mean percentage change in IGF-1 concentration from baseline was -4.0%, -26.7%, -50.1% and -62.5% for the placebo, pegvisomant 10mg, 15mg and 20mg groups, respectively. This change was statistically significant for all groups versus placebo, for pegvisomant 15mg and 20mg versus pegvisomant 10mg and for pegvisomant 20mg versus pegvisomant 15mg.

In the second study, the mean changes in IGF-1 and GH for the 6, 12, and 18 month cohorts were -467 µg/L and +12.5 µg/L, -526 µg/L and +12.5 µg/L, and -523 µg/L and +14.2 µg/L, respectively. During treatment with pegvisomant for =12 months, 97% and 92% of patients had normal IGF-1 concentrations with doses up to 40mg/day and 30mg/day, respectively. Paired sets of baseline and the most recent MRI scans were available for 131 patients with a mean duration from baseline to final scan of 11.46 months. The mean change in tumour volume from baseline was -0.033cm, p=0.353.

Secondary endpoints, sub-group analysis and uncontrolled trials

In the first study the percentage of patients with a normal IGF-1 concentration at 12 weeks was 9.7%, 38.5%, 75.0% and 82.1% for the placebo, pegvisomant 10mg, 15mg and 20mg groups, respectively and was statistically significant for all pegvisomant groups versus placebo. A statistically significant decrease in ring size was observed for the pegvisomant 15mg and 20mg groups versus placebo. The mean scores for the individual symptoms and signs and the mean total score increased slightly in the placebo group and decreased in all pegvisomant groups, with significant decreases in the scores for soft tissue swelling, perspiration and fatigue.

Summary of evidence on comparative safety

In the long-term study of pegvisomant, 160 patients were included in the safety analysis. Adverse effects, reported in more than 10% of patients, included; headache (26%), infection (33%), pain (23%), influenza-like syndrome (21%), injection site reaction (11%), back pain (13%), asthenia (13%), accidental injury (18%), diarrhoea (14%), sinusitis (10%), hypercholesterolaemia (14%) and arthralgia (12%). Two patients had increases in alanine aminotransferase and aspartate aminotransferase of more than ten times the upper limit of normal within 12 weeks of initiation of pegvisomant. Liver enzymes returned to normal within months of stopping pegvisomant. The Summary of Product Characteristics for pegvisomant recommends that serum concentrations of alanine aminotransferase (ALT) and aspartate transaminase (AST) should be monitored at four to six week intervals in the first six months following initiation of pegvisomant or at any time in patients exhibiting symptoms suggestive of hepatitis.

Summary of clinical effectiveness issues

Although the mean tumour volume did not change significantly over the 11.5 months of treatment, an editorial published in the Lancet at the same time as the second study does warn that patients who have not received radiotherapy, should be closely monitored for tumour growth while on pegvisomant. Monitoring of tumour size is recommended in the Summary of Product Characteristics for pegvisomant under special warnings.

There are limited published data on the use of pegvisomant with somatostatin analogues, although this combination is the focus of a current clinical trial. The concomitant use of somatostatin analogues with pegvisomant requires careful consideration.

According to epidemiological evidence, GH concentration is the most important determinant of mortality in acromegaly, and this is supported by a consensus statement on criteria for cure of acromegaly, which strongly recommended tight control of GH concentrations. This is not possible for patients being treated with pegvisomant. There is a tight physiological relationship between GH and IGF-1 in acromegaly, which suggests that IGF-1 may be a surrogate marker for GH activity. However, a concern has been raised with the finding that IGF-1 may be normal in up to 50% of patients with GH deficiency, resulting in difficulties in detecting unintentional over-treatment. The author concluded, that a safe target range for IGF-1 needs to be defined through long-term prospective studies.

The preparation of the injection requires reconstitution of the pegvisomant powder with solvent (water for injections). The solvent is added to the pegvisomant vial and the powder allowed to dissolve using a slow swirling movement. Some patients may find this procedure cumbersome, which could potentially result in poor compliance.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis that estimated the long-term cost per QALY gained in comparison to somatostatin analogues to be £105k. The key assumptions were that normalised IGF-1 levels result in better quality-of-life through reduced symptoms and eliminate the excess risk of premature mortality.

The evaluation rests upon trial data that are relatively short-term in the context of a lifetime of disease treatment. This forces the manufacturer to assume efficacy rates seen at up to 18 months of follow-up can be maintained for around 40 years (patient lifetime). Similarly, quality-of-life gains, which have only been demonstrated at 12 weeks follow-up, are assumed to last for a lifetime if treatment continues.

In addition, the short-term nature of the trials meant that the manufacturer had to assume that the survival benefits from IGF-1 normalisation following surgery would also apply following treatment with pegvisomant. Expert clinician advice suggests that, while this is plausible, the relative risk reduction assumed could be an over-estimate.

The cost per QALY submitted by the manufacturer is high and if the mortality benefit has been overestimated the true figure could be even higher.

Budget impact

The budget impact, after allowing for savings on somatostatin analogues, is estimated to be £131k in year 1 rising to £218k in year 5. This is based on an assumption of 31 patients with uncontrolled acromegaly in Scotland and a market share of 30% in year 1 rising to 50% in year 5.

Guidelines and protocols

The protocol for a Cochrane systematic review of the pharmacological treatment of acromegaly was first published in 2002 and updated in 2004.

A consensus statement on the criteria for cure of acromegaly was published in 2000.[5] A definition of cure as well as treatment outcomes (controlled, inadequately controlled and poor control) were agreed. The lowering of the GH/IGF-1 indices as close to “normal” as clinically possible was crucial.

Additional information

There are two ongoing pegvisomant studies being conducted by Pfizer Ltd. The first study is comparing the safety and tolerability of combination (sandostatin LAR plus pegvisomant) therapy to Sandostatin LAR alone or pegvisomant alone. The aim of the second study is to determine if pegvisomant is more efficacious than sandostatin LAR in normalising IGF-1 levels in treatment naïve patients with acromegaly.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 10 January 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

1. *Trainer PJ, Drake WM, Katznelson L. et al., Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. New England Journal of Medicine 2000; 342(16):1171-7.*

2. *van der Lely AJ, Hutson RK, Trainer PJ et al., Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. The Lancet. 2001; 24; 358 (9295):1754-9.*

3. *European Agency for the Evaluation of Medicinal Products (EMEA) Somavert European Public Assessment Report (EPAR) scientific discussion (accessed on http://www.emea.eu.int/humandocs/Humans/EPAR/somavert/somavert.htm)*

4. *Giustina A, Barkan A, Casanueva F et al. Criteria for cure of Acromegaly: A Consensus Statement. Journal of Clinical Endocrinology and Metabolism. 2000; 85: 526-529*

5. *Ho K. Place of pegvisomant in acromegaly (editorial). The Lancet 2001; 358: 1743-1744*