National PBM Drug Monograph/Class Review

Pegvisomant for injection (Somavert®)

September 2003

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary

- Pegvisomant, a highly selective GH receptor antagonist, offers a significant advancement in the treatment of acromegaly, a serious, life-shortening disease. Unlike dopamine agonists and somatostatin analogs, both of which inhibit GH secretion, pegvisomant modifies hormone action by blocking GH-stimulated, hepatic production of IGF-1, the main mediator of the somatotrophic actions of GH.

- Pegvisomant is very efficacious. It achieves the highest rate of IGF-1 normalization (93% to 97%) compared with historical rates for somatostatin analogs and dopamine agonists. It is probably the most effective medical therapy available for acromegaly, either as a first- or second-line drug.

- The main safety concern with pegvisomant is abnormal liver tests, although renal toxicity is pronounced in animal studies. Hepatotoxicity, manifested mainly as reversible increases in serum aminotransferases, occurred in 2 (1.2%) of 160 patients with acromegaly who were exposed to pegvisomant in clinical trials (0.8% of 241 study subjects exposed to the drug). Rigorous monitoring of liver tests is required during pegvisomant therapy.

- GH concentrations increase by two- to three-fold, but not progressively, as a result of decreased IGF-1 concentrations. There is no clear evidence that pegvisomant stimulates tumor growth by increasing GH concentrations. However, pegvisomant would not be able to stop further tumor enlargement, unlike somatostatin analogs, which may even shrink tumor size.

- Pegvisomant should be reserved for second-line drug therapy in patients who have had an inadequate response to or are not appropriate candidates for surgery and/or radiation therapy, and who also have had an inadequate response to maximal doses of somatostatin analogs with or without dopamine agonists, or who have documented intolerance or hypersensitivity to somatostatin analogs. Combination therapy with pegvisomant and somatostatin analogs may be rational in patients who meet the above criteria and also have rapidly growing tumors. In this subset of patients, the somatostatin analog may prevent tumor growth while pegvisomant normalizes serum IGF-1 concentrations.

- The only method of obtaining pegvisomant is through Pfizer's Bridge Program, which limits access to the drug by providing the medication directly to the patient based on payment contracts.

Introduction

Usual therapies for acromegaly consist of transphenoidal surgery, radiotherapy, analogs of the GH–inhibitory hormone, somatostatin (octreotide and lanreotide), and dopamine agonists (bromocriptine and cabergoline). Drug therapy is usually used for surgical failures and/or after radiotherapy while waiting for a clinical effect. While these therapies are presently the standard of care, they do not produce an adequate response in about 30% to 40% of patients.[1]

Pegvisomant, a highly selective GH receptor antagonist that is the first drug of this class to be developed, offers a novel approach to treatment of acromegaly, a serious, life-shortening disease. Whereas conventional medical therapies (somatostatin analogs and dopamine agonists) aim to correct excessive GH secretion, the primary aim of therapy with pegvisomant is to decrease and normalize concentrations of IGF-1, the main mediator of GH action. The FDA granted pegvisomant Orphan Drug status and designated it for Priority Review in 2001, and approved it for treatment of acromegaly in March 2003. Its usefulness in other indications is also being studied. A phase IIa trial found pegvisomant ineffective for diabetic retinopathy.[20] Phase I trials have been started to explore the efficacy of pegvisomant for nephropathy.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating pegvisomant for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Mechanism of action

Pegvisomant is a pegylated analog of genetically altered human GH that binds to the GH receptor, blocks the binding of endogenous GH, and prevents dimerization of adjacent GH receptors. It thereby blocks GH-stimulated, hepatic production of IGF-1, the main mediator of the somatotrophic actions of GH. Unlike somatostatin analogs, which require functional somatostatin receptors to be present on GH-secreting pituitary adenomas, pegvisomant effects are independent of tumor characteristics. It is also very highly selective for the GH receptor, and does not cross-react with other receptors, including the prolactin receptor.

Absorption, distribution, metabolism, and elimination

Pegvisomant has a rapid onset of action. In the major efficacy trial by Trainer et al., 75 percent or more of the maximal reduction in serum IGF-1 concentrations occurred within 2 weeks of initiating treatment with a loading dose of pegvisomant 80 mg followed by 10, 15, or 20 mg per day subcutaneously.[2] In comparison, IGF-1 concentrations normalize only several months after surgery and initiation of conventional medical therapies.[3]

Pegylation (covalent binding of polyethylene glycol polymers to the protein) decreases renal clearance, thereby prolonging the elimination half-life and activity of pegvisomant.

The pharmacokinetic parameters of pegvisomant are shown in Table 1.

Table 1 Pharmacokinetic parameters of pegvisomant

Time to C_{max}	33 to 77 h
Bioavailability	57%
Protein Binding	Not available
Clearance	Decreases with multiple doses vs. single doses; increases with body weight
Metabolism	Not available
Elimination	Route of elimination not studied in humans; < 1% recovered in urine over 96 h
Half-life	6 days

FDA Approved Indication(s) and Off-label Uses

FDA approved indication

Treatment of acromegaly in patients who have had an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are not appropriate.

Off-label use

Combination therapy with pegvisomant and a somatostatin analog may be useful in patients who do not obtain an adequate response to surgery and/or radiotherapy and a somatostatin analog with or without a dopamine agonist who have a rapidly growing pituitary tumor. Pegvisomant would be used to decrease or normalize IGF-1 concentrations and the somatostatin analog would be used to prevent tumor growth. Support for this use comes from one case report.[4]

Current VA National Formulary Status

Nonformulary, new molecular entity

Dosage and Administration

Patients will need to be taught how to properly inject, reconstitute, and store pegvisomant.

Initiation and titration

Loading dose:	40 mg s.c.[a] under physician supervision
Initial maintenance dose:	10 mg s.c. daily
Increments or decrements:	5 mg.
Maximum maintenance dose:	30 mg daily

IGF-1 concentrations should be measured 4 to 6 weeks after starting therapy and after any dosage adjustments, and at least every 6 months after IGF-1 concentrations have normalized. Dosage increments or decrements of 5 mg per day should be based on serum IGF-1 concentrations. It is not known if patients who remain symptomatic despite normal IGF-1 concentrations would benefit from increasing the dose of pegvisomant.

Reconstitution and storage

Pegvisomant is available as a lyophilized powder that must be reconstituted with the diluent (Sterile Water for injection) supplied in the package. Vials of dissolved pegvisomant powder should be rolled and not shaken, as shaking may cause denaturation of the drug. Further details about reconstitution are available in the package insert (available at: http://somavert.com).

Before reconstitution, pegvisomant should be refrigerated at 2 to 8°C and protected from freezing. Doses should be administered within 6 hours after reconstitution.

Special populations

No pharmacokinetic studies have been conducted in patients with renal or hepatic insufficiency, elderly patients, and pediatric patients. In elderly patients, use caution; doses should usually be started at the low end of the dosing range.

No gender effect on the pharmacokinetics of pegvisomant was found in a population pharmacokinetic analysis. The effect of race has not been studied.

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[a] The package insert recommends a smaller loading dose than the 80-mg loading dose used in the major efficacy trial by Trainer et al.[5] The FDA approved a 40-mg loading dose based on the results of a small, unpublished trial that found comparable pharmacokinetic and pharmacodynamic characteristics, as well as very similar clinical efficacy and safety endpoints with the 80- and 40-mg loading doses. The FDA felt that any differences between patients receiving either loading dose are not clinically significant, considering the chronicity of the disease and infrequent intervals recommended for dosage adjustments (6 to 8 weeks). The FDA also recommended that after drug approval the sponsor conduct a small pharmacokinetic-pharmacodynamic study to evaluate the need for a loading dose.

Distribution Through Bridge Program

The only method of obtaining pegvisomant is through Pfizer's Bridge Program, a specialty pharmacy and reimbursement assistance program that provides the drug directly to the patient, although Pfizer may ship to pharmacies for Medicaid patients in certain states (Delaware, Florida, Massachusetts, New Jersey, North Carolina, Texas, Tennessee, and West Virginia). Physicians must fax a Statement of Medical Necessity (SMN), which includes prescription details, to the Bridge Program at (800) 479-2562. Depending on the patient's health insurance coverage, a payment contract is prepared for each patient and must be reviewed and approved by Pfizer. The Bridge Program provides only enough drug for the prescribed duration of therapy. Supplemental SMNs, along with IGF-1 results, must be submitted for refills. For further details and SMN forms, go to: http://www.somavert.com.

Somavert® Patient Registry

At the time of the FDA medical review in February 2003, Pharmacia and Upjohn agreed to develop a registry of patients on pegvisomant in order to carefully follow safety and to assess durability of efficacy. The FDA recommended that safety end points should include, in particular, liver transaminases, pituitary tumor size, renal function/urinalyses, and immunogenicity. The drug was approved in March 2003. In April, Pfizer acquired Pharmacia. No further details about the patient registry were available from Pfizer's medical information department. [It is possible that the registry will become an extension of the Bridge Program.]

Adverse Events (Safety Data)

Overall, pegvisomant has a satisfactory safety profile. According to the FDA medical reviewer, pegvisomant may be superior to somatostatin analogs in safety (and efficacy), although no direct comparison of the two treatments has been performed.

Serious Adverse Events

There were no reports of deaths or anaphylaxis in published clinical trials.

The main safety concern with pegvisomant is abnormal liver tests. Hepatotoxicity, manifested mainly as reversible increases in serum ALT and AST to more than 10 times the upper limit of normal, developed in 2 (0.8%) acromegalic patients of a total 241 subjects exposed to pegvisomant during clinical trials (including 160 patients with acromegaly, 45 patients with diabetes mellitus, and 36 healthy volunteers). One patient re-developed increased ALT and AST upon rechallenge with pegvisomant, suggesting a probable causal relationship with the drug. The other patient had a liver biopsy that was consistent with chronic hepatitis of unknown etiology. In this latter case, the causal relationship with pegvisomant is possible.

Smaller increases in transaminases (ALT greater than 3 times but less than or equal to 10 times the upper limit of normal) were seen in 1.2% of acromegalic patients on pegvisomant and 2.1% of patients on placebo. The increases in transaminases did not appear to be dose-related, generally occurred within 4 to 12 weeks of initiation of therapy, and were not associated with any identifiable biochemical, phenotypic, or genetic predictors. Concurrent increases in serum total bilirubin and alkaline phosphatase were not observed, with the exception of two patients with

increases in alkaline phosphatase less than 3 times the upper limit of normal. In many cases, the increases in transaminases were sporadic or returned to normal on pegvisomant.[1]

In a Periodic Safety Update Report covering the period from 1 June 2000 to 18 July 2002, urinary incontinence was reported as a new serious adverse event in 1 of 25 patients exposed to pegvisomant.[1] All of these patients had been enrolled in the open-label extension studies prior to 1 June 2000.

Common Adverse Events

The frequency of adverse events was similar in the pegvisomant and placebo groups, with the exceptions of infection, injection site reaction, flu syndrome, diarrhea, and nausea, in which the frequency of the adverse event was 10% or greater for any pegvisomant group than the placebo group (see table below).

Adverse events that occurred in at least 2 patients and at a higher rate on pegvisomant than on placebo in a 12-week study

		Pegvisomant (mg/d)		
	Placebo	**10**	**15**	**20**
Description	N = 32	N = 26	N = 26	N = 28
Body as a whole				
Infection†	2 (6)	6 (23)	0	0
Pain‡	2 (6)	2 (8)	1 (4)	4 (14)
Injection-site reaction	0	2 (8)	1 (4)	3 (11)
Accidental injury	1 (3)	2 (8)	1 (4)	0
Back pain	1 (3)	2 (8)	0	1 (4)
Flu syndrome	0	1 (4)	3 (12)	2 (7)
Chest pain	0	1 (4)	2 (8)	0
Digestive system				
Abnormal liver function tests	1 (3)	3 (12)	1 (4)	1 (4)
Diarrhea	1 (3)	1 (4)	0	4 (14)
Nausea	1 (3)	0	2 (8)	4 (14)
Nervous system				
Dizziness	2 (6)	2 (8)	1 (4)	1 (4)
Paresthesia	2 (6)	0	0	2 (7)
Metabolic and nutritional disorders				
Peripheral edema	0	2 (8)	0	1 (4)
Cardiovascular system				
Hypertension	0	0	2 (8)	0
Respiratory system				
Sinusitis	1 (3)	2 (8)	0	1 (4)

Source: Somavert® Package Insert

† Infection: included cold symptoms (3 patients), upper respiratory infection (1 patient) blister (1 patients) and ear infection (1 patient) in the pegvisomant 10-mg group, and cold symptoms (1 patient) and chest infection (1 patient) in the placebo group.

‡ Included pain in the scalp, neck, shoulders, arms, and legs.

During pegvisomant therapy for up to 18 months, the top five most frequent adverse events were infection, headache, pain, influenza-like syndrome, and accidental injury.[6]

According to the FDA medical review, the treatment-emergent adverse event most likely related to pegvisomant was injection site reaction.[1] In addition, the only severe treatment-emergent adverse event seen in 5% or more of study patients with acromegaly was headache, seen in the pegvisomant groups.

Other adverse events

Additional safety issues include the following:

- *Secretion and action of GH.* As a result of decreased IGF-1 concentrations, GH concentrations increase substantially, peaking in about 2 weeks after initiation of pegvisomant, but do not progressively increase over an 18-month period. There was concern that GH concentrations might increase with prolonged therapy and that it could stimulate tumor growth. In addition, persistent GH excess might theoretically counteract the receptor-blockade of pegvisomant. There was no evidence of tumor growth or loss of efficacy in a long-term clinical trial lasting up to 18 months (mean: 14 months).

- *Tumor growth.* Although there is so far no clear evidence that pegvisomant stimulates tumor growth by increasing GH concentrations, in an 18-month study, there was a statistically nonsignificant, slight increase in tumor volumes in patients without prior radiotherapy and decrease in tumor volumes in patients who had received prior radiotherapy.[6] Longer studies may be needed to detect extension of slow-growing pituitary tumors. In clinical trials, two patients, who had large globular tumors impinging on the optic chiasm at baseline, manifested rapid tumor growth on pegvisomant. Unlike somatostatin analogs, which may abort further tumor enlargement, pegvisomant would not have the same advantage, particularly in non-irradiated patients with aggressive tumors.[7]

- *Glucose tolerance*. Pegvisomant may improve glucose tolerance, which could result in hypoglycemia. In clinical trials, none of the patients with diabetes mellitus who were treated with pegvisomant had clinically relevant hypoglycemia.[8]

- *GH deficiency state*. A state of functional GH deficiency may result from pegvisomant therapy, despite increased GH concentrations. Inadvertent overtreatment is a concern with pegvisomant because about 50% of adults with GH deficiency have normal IGF-1 concentrations.[9] Since monitoring of GH concentrations is not possible with pegvisomant, it has been suggested that further studies are needed to define a safe IGF-1 target range for monitoring pegvisomant treatment.[7] Currently, age-adjusted normal limits for IGF-1 are recommended as the target range.

- *Potential polyethylene glycol (PEG)–-induced renal toxicity.* Histologic tubulopathy of uncertain etiology was observed during preclinical studies in female rats only. The package insert for pegvisomant currently does not recommend routine monitoring of renal function because no renal safety signal was observed during clinical trials. The FDA recommended that the Somavert® patient registry follow renal function of patients because nephrotoxicity of unknown etiology was observed during preclinical rat studies and renal toxicity has been associated with other PEG-containing drugs.

- *Bone turnover*. Pegvisomant treatment decreases the serum concentrations of markers of bone formation (osteocalcin and procollagen I carboxy-terminal propeptide [PICP]) and resorption (N-telopeptide [NTx]), coincident with decreases in IGF-1.[10] The long-term effects on bone mineral density are uncertain. It is possible that the increased concentrations of GH seen with pegvisomant therapy may have an independent effect on bone turnover.

- *Cardiovascular effects*. No studies have reported beneficial or adverse cardiovascular effects in association with pegvisomant therapy. A *post hoc* substudy[11] evaluated cardiovascular risk markers in patients who participated in the phase III placebo-controlled trial by Trainer et al.[5] and the follow-on longitudinal open-label study.[6] The authors found that C-reactive protein (CRP, considered to be an inflammatory and cardiovascular risk marker) concentrations are low in patients with acromegaly (despite the association of acromegaly with cardiovascular disease) and that pegvisomant increases concentrations of CRP as compared with placebo and healthy controls. The mechanism and pathophysiologic significance of these findings are yet to be elucidated.

- *Hydrocortisone requirements*. GH inhibits 11 [beta]-hydroxysteroid dehydrogenase and reduces conversion of cortisone to cortisol. A small, uncontrolled, open-label study (N = 7) showed that pegvisomant (20 mg per day for a mean of 46 weeks) normalizes cortisol metabolism by reversing GH-induced inhibition of the enzyme.[12] The urinary 11-hydroxy-to-11-oxo cortisol metabolite ratio increased from 0.61 to 0.88 ($p < 0.02$) The urinary tetrahydrocortisol-to-tetrahydrocortisone ratio increased from 0.64 to 0.98 ($p < 0.02$). It is possible that fixed-dose hydrocortisone may result in overtreatment of pegvisomant-treated patients with adrenocortical insufficiency.

Tolerability

Pegvisomant is generally well tolerated. Withdrawals due to adverse events occurred in 9 (9.6%) of patients in major efficacy trials, including two patients with increases in liver transaminases (for further details, see tabulated summaries of clinical trials, pages 12 and 17).

Precautions/Contraindications

Precautions

Liver dysfunction. Rigorous monitoring of liver tests is required during pegvisomant therapy. Liver tests should be monitored at baseline, monthly for the first 6 months, quarterly for the next 6 months, then biannually for the next year. A comprehensive hepatic workup should be performed if liver test values exceed 3 times the upper limit of normal or the patient develops signs or symptoms suggestive of hepatitis or other liver injury. Specific recommendations for the use of pegvisomant in patients with increases in liver test values are given in the package insert (available at: http://www.somavert.com). Since many patients with acromegaly develop hyperlipidemia, extra caution may be warranted in patients treated with HMG-CoA reductase inhibitors, as these agents are also hepatotoxic.

Tumor growth. All patients with pituitary tumors, including those on pegvisomant, should be monitored for possible tumor growth with periodic imaging scans of the sella turcica.

Glucose metabolism. Glucose tolerance may increase in some patients, necessitating monitoring for hypoglycemia and modification of dosage if necessary.

GH deficiency. Patients should be monitored for clinical signs and symptoms of a GH deficiency state and the pegvisomant dose should be titrated to keep IGF-1 concentrations within the age-adjusted normal range.

Use in pregnancy and lactation. Category B. Use pegvisomant during pregnancy only if clearly needed. Exercise caution when pegvisomant is taken by a nursing woman, as it is not known if pegvisomant is excreted in human milk.

Contraindications

Pegvisomant should not be used in patients with a hypersensitivity to any components. The stopper on the vial of pegvisomant contains latex.

The use of pegvisomant is not recommended in patients with baseline liver tests greater than 3 times the upper limit of normal without a comprehensive workup to establish the cause of liver dysfunction. Its use may be considered once the cause is determined.

Pegvisomant should be discontinued in patients who develop increases in liver test results at least 5 times the upper limit of normal or transaminase values at least 3 times upper limit of normal associated with any increase in serum total bilirubin with or without signs or symptoms of hepatitis or other liver injury.

Drug Interactions

Drug-drug interactions

Study patients on opioids often needed higher serum pegvisomant concentrations to achieve appropriate IGF-1 suppression compared with patients not receiving opioids. The mechanism of the interaction is unknown.

Drug-lab interactions

Since pegvisomant is structurally similar to GH, it interferes with commercially available GH assays. At usual therapeutic doses, serum concentrations of pegvisomant are generally 100 to 1000 times higher than endogenous GH concentrations. The FDA recommended that GH concentrations be monitored during dosage titration and once a maintenance dose was achieved to detect rapid or progressive increases that might signal rapid growth of the GH-secreting pituitary adenoma. Currently, however, there is no commercially available assay for GH that does not interact with pegvisomant.

Efficacy Measures

IGF-1. IGF-1 is the principal marker of disease activity in acromegaly. Serum concentrations of IGF-1 have been shown to correlate with clinical and biochemical markers of disease activity.[13] Normalization of IGF-1 is associated with resolution of symptoms and normal life expectancy.[14]

Signs and symptoms of acromegaly. Improvement in signs and symptoms of acromegaly (soft tissue swelling, arthralgia, headache, excessive perspiration, and fatigue) are expected to have a direct relationship with IGF-1 concentrations, although improvement in symptoms can occur with decreases in IGF-1 without normalization.

Ring size. Standardized measurements of the fourth digit of the right hand are used as an indicator of soft tissue swelling.

Pituitary tumor size. Pegvisomant treatment results in relatively small, nonprogressive increases in GH concentrations as a consequence of the decreases in IGF-1. Enlargement of the tumor due to increased secretion of GH may compromise the efficacy of pegvisomant as well as pose a potential safety problem.

Clinical Trials

Most of the information on clinical trials was obtained from two published, major efficacy trials, the Somavert® package insert, data discussed in the FDA medical review of pegvisomant,[1] and Pfizer's AMCP-Formatted[b] Formulary Submission Dossier (dated May 29, 2003). The published and unpublished clinical trials reported to the FDA consist of a 12-week, placebo-controlled, randomized, double-blind, multicenter study (N = 112, 80 patients exposed to pegvisomant); and two long-term, open-label, dose-titration studies of patients on daily pegvisomant for at least 12 consecutive months (N = 38) or up to 18 months (N = 152). Several substudies and case reports involving patients who participated in the major efficacy trials were also reviewed.[4,15-17]

Summary of efficacy findings

In contrast to somatostatin analogs, which can normalize GH and IGF-1 concentrations as well as shrink tumors,[18] the primary efficacy response to pegvisomant treatment is a decrease or normalization of IGF-1 concentrations accompanied by improvement or resolution of symptoms, including soft tissue swelling and general well-being.

Pegvisomant achieves the highest rate of IGF-1 normalization compared with historical rates for somatostatin analogs and dopamine agonists. Although a direct comparison between pegvisomant and the other available agents has not been performed, the FDA medical reviewer agreed that well documented historical data and retrospective analyses of pegvisomant clinical trial data suggest that pegvisomant is superior.[1] These data include the following:

- IGF-1 normalization was achieved in 93% and 97% after at least 12 to 18 months of daily pegvisomant treatment compared with a mean of 54% for 15 somatostatin analog studies, despite a lower baseline IGF-1 concentration in the somatostatin analog studies. [Rates for long-acting octreotide are about 66% (range 41% to 75%) over a mean of 20 months.[19]] Dopamine agonists achieve normal GH and IGF-1 concentrations in less than 20% of patients.[1]

[b] AMCP, Academy of Managed Care Pharmacy

- A subset of 13 somatostatin analog–resistant patients achieved normalization of IGF-1 concentrations with pegvisomant.

- Another subset of 44 somatostatin analog–treated patients, who were enrolled in the 12-week placebo-controlled trial of pegvisomant,[5] had an IGF-1 normalization rate of 38.6% prior to switching to pegvisomant, whereas it was 93.2% after pegvisomant therapy.

Rates of withdrawal due to lack of efficacy are low—2 (1.8%) of 112 patients who received pegvisomant for 12 weeks,[5] and 5 (3.1%) of 160 patients treated for up to 18 months.[6]

Pegvisomant shows durability of efficacy for up to 18 to 24 months; however, this evidence is based on a small number of patients, and may not reflect durability of efficacy for longer periods.

GH concentrations increase in a dose-dependent manner by two- to three-fold in the first two weeks of therapy, and appear to be related to the magnitude of decrease in IGF-1. GH concentrations do not increase further with longer therapy of up to 18 months.

Tumor size remains stable up to 18 months of pegvisomant therapy.

Two case series have documented 100% efficacy in a subset of patients resistant to a somatostatin analog and/or dopamine agonist. In the first report, 6 patients who had not responded to maximal doses of octreotide achieved normal IGF-1 concentrations with pegvisomant 30 to 80 mg per week for 6 weeks then 10 to 20 mg per day for 1 year (N = 3) or 10 to 30 mg per day for 4 to 9 months (N = 3).[15] The second case series included 7 patients who were refractory to standard adjunctive medical therapy with a somatostatin analog and/or dopamine agonist following primary therapy with surgery and/or radiotherapy. All patients achieved normal IGF-1 concentrations and improvement in signs and symptoms on pegvisomant 15 to 40 mg per day (mean: 20 mg).[16] Efficacy was maintained after 2 years.

Combined therapy with pegvisomant and octreotide has been suggested to normalize IGF-1 concentrations with pegvisomant in a subset of patients who do not obtain complete biochemical responses with somatostatin analogs, but who have rapidly growing tumors that might benefit from the tumor growth–suppressing effects of somatostatin analogs. Combination therapy (pegvisomant and long-acting somatostatin) was found to be beneficial in a single such case during the clinical trials.[4] No other study patients required combination therapy to normalize IGF-1 concentrations. Routine combination therapy is probably not necessary because the efficacy of pegvisomant is so high that there would be few patients who would require addition of a somatostatin analog to achieve IGF-1 normalization. Similarly, very few patients resistant to somatostatin analogs do not respond to pegvisomant alone.

Pegylation of the GH protein reduces the likelihood of antibody formation but pegvisomant has at least weak immunogenic potential. In clinical trials, 27 (16.9%) of 160 study patients developed low-titer, non-neutralizing anti-GH antibodies during treatment and 27 (16.9%) of 160 patients had anti-pegvisomant antibodies detected 1 month after discontinuation of drug. Although the efficacy of pegvisomant did not appear to be affected by either of these antibodies for up to 18 months, the long-term effects are unknown. There are currently no commercially available assays for these antibodies. (Also see drug-lab interactions on page 9.)

An open-label, uncontrolled study (N = 20) showed that pegvisomant-induced normalization of IGF-1 is associated with normalization of total cholesterol and low-density lipoprotein concentrations, which are decreased in acromegaly.[17]

Efficacy outcomes that have not been assessed include disease-associated mortality and morbidity (cardiovascular disease, diabetes mellitus, respiratory dysfunction, rheumatoid disorders, sleep apnea, and premalignant colonic polyps), and quality of life. In addition, efficacy after very long-term use (greater than 18 to 24 months) has not been evaluated.

Summaries of published, major clinical trials

Citation	**Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. NEJM 2000 Apr 20;342(16):1171-7**
Study Goals	To study the efficacy and tolerability of pegvisomant in patients with acromegaly
Methods	• **Study Design** ➢ Phase III, multicenter, multinational (Germany, Netherlands, Sweden, UK, and US), double-blind, placebo-controlled RCT of three doses of pegvisomant (80-mg bolus followed by 10, 15, or 20 mg per day subcutaneously) given over 12 weeks (Protocol SEN-3614/15) ➢ Previous medical therapy was withdrawn 2 or more weeks after the initial screening visit for short-acting somatostastin analogs, 5 or more weeks for dopamine agonist therapy, and 12 or more weeks for long-acting somatostatin analogs. ➢ Patients were stratified according to serum insulin growth factor-I (IGF-1) concentration before randomization (1.3 to 2.0 times the upper limit of the age-adjusted normal range vs. > 2.0 times the upper limit) ➢ Primary efficacy end point: percentage change in serum IGF-1 concentration from base line. ➢ Other efficacy variables: 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, incapacitating symptoms) ➢ Safety measures: anti-GH antibodies, hematology, serum chemistry, urinalysis, adverse events, tumor volume determined on MRI of pituitary, electrocardiogram ➢ GH concentrations were measured by radioimmunoassay modified to avoid cross-reactivity with pegvisomant

	• **Data Analysis** ➢ No power calculation was reported ➢ Statistical analysis of primary efficacy variable: analysis of variance (ANOVA) with study sites pooled according to geographic area; an expanded statistical model was used to test for the interaction between treatment and center as well as covariates (baseline serum IGF-1, GH, IGF-1 values at study entry, sex, and baseline body weight) ➢ Other statistical analyses: ANOVA for continuous variables; logistic regression model for comparison of frequency of normal serum IGF-1 concentration at any time after baseline and at 12 weeks, with independent variables of treatment, pooled study site, and baseline IGF-1; Cochran-Mantel-Haenszel test for other scheduled visits (at 2, 4, and 8 weeks); extended Cochran-Mantel-Haenszel test for comparison of signs and symptoms (categorized as worse, unchanged, or improved), with adjustment for pooled study site
Criteria	• **Inclusion criteria** ➢ 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 • **Exclusion criteria** ➢ Treatment with a long-acting somatostastin analog within 12 weeks before enrollment
Results	• 112 patients enrolled and received study medication; 63 men, 49 women; mean age (± SD): 48 ± 14 years; mean duration of acromegaly: 8 ± 8 years. Baseline characteristics were similar between treatment groups. • Prior surgery with radiotherapy (57 of 112 enrolled patients), pituitary surgery only (36 patients), radiotherapy without surgery (6 patients), drug therapy only (9 patients), or no prior therapy (4 patients). Previously treated with somatostatin analog (81 patients), dopamine agonist (55 patients). • 4 patients withdrew: 2 from placebo group (1 because of persistent headache, classified as lack of efficacy; 1 because of tumor compression of optic chiasm noted on MRI after 5 days of treatment, excluded from efficacy analysis because no efficacy assessments had been made before withdrawal) and 2 from pegvisomant group (1 because of persistent headache after 5 days of therapy with pegvisomant 15 mg/day, classified as lack of efficacy; 1 because of high serum aminotransferases after 9 weeks of therapy)

Efficacy:

Selected efficacy measures

Variable	Placebo N = 31[†]	Pegvisomant (mg/d) 10 N = 26	15 N = 26	20 N = 28
Baseline IGF-1(ng/ml)	670 ± 288	627 ± 251	649 ± 293	732 ± 205
12-wk IGF-1 (ng/ml)	640 ± 288	449 ± 220	321 ± 203	279 ± 183
Change in IGF-1 (%) [PEV]	–4.0 ± 16.8	–26.7 ± 27.9*	–50.1 ± 26.7**	–62.5 ± 21.3***
Tx difference (PGV – PBO) (mean, 95% CL)	—	–23 (–35, –11)	–44 (–56, –33)	–59 (–68,–49)
IGF-1 WNL, n (%)	3 (10)	14 (54)*	21 (81)*[‡]	25 (89)*
Baseline GH (ng/ml)	8.7 ± 20.1	7.8 ± 10.5	11.5 ± 23.1	8.1 ± 10.6
12-wk GH (ng/ml)	7.6 ± 15.1	10.5 ± 11.8	21.4 ± 22.7	22.7 ± 27.8
Change in GH (ng/ml)[§]	–0.8 ± 5.0	2.7 ± 5.5****	9.2 ± 10.6*	14.4 ± 21.2*
Baseline tumor vol. (ml)	1.9 ± 1.8	2.4 ± 2.6	3.3 ± 6.1	2.1 ± 1.9
12-wk tumor vol. (ml)	1.8 ± 1.8	2.4 ± 2.6	3.4 ± 6.3	2.2 ± 2.0

Source of Treatment (Tx) Difference: Somavert® Package Insert[8]. Other values taken from the published report.

Values shown as mean ± SD; GH = Growth hormone; IGF-1 = Insulin growth factor-I; PBO = Placebo; PEV = Primary Efficacy Variable; PGV = Pegvisomant; WNL = Within normal limits (at any visit after baseline)

* $p < 0.001$ vs. placebo

** $p < 0.001$ vs. placebo and $p = 0.005$ vs. 10 mg pegvisomant

*** $p < 0.001$ vs. placebo, $p < 0.001$ vs. 10 mg pegvisomant, and $p = 0.02$ vs. 15 mg pegvisomant

**** $p = 0.08$ vs. placebo

† Efficacy data excludes one patient who withdrew before the first evaluation after baseline

‡ Excludes two patients who withdrew before week 12

§ Values are the means of individual changes

- Serum IGF-1 concentrations decreased from baseline to week 12 in all three pegvisomant groups, and did not significantly change in the placebo group. No interaction with study site was detected.

- The frequency of normal IGF-1 concentrations, detected at any visit after baseline, showed a dose-dependent increase in the pegvisomant groups, ranging from 54% to 89%, whereas normal IGF-1 was seen in 10% of the placebo group. According to the FDA Medical Review of this study, 47 (58.8%) of 80 pegvisomant-treated patients achieved normalization of IGF-1 within just 2 weeks.

- IGF-1, free IGF-1, IGFBP-3, and the acid-labile subunit of IGFBP-3 also showed significant dose-dependent decreases in the pegvisomant groups ($p \leq 0.05$ for all four measures; data not shown here).

- Mean scores for signs and symptoms of acromegaly are shown in the table below.

Change from baseline at Week 12 in signs and symptoms of acromegaly

		Pegvisomant (mg/d)		
	Placebo	10	15	20
Variable	N = 31[†]	N = 26	N = 26	N = 28
Ring size	–0.1 (2.3)	–0.8 (1.6)	–1.9 (2.0)*	–2.5 (3.3)*
Total score	1.3 (6.0)	–2.5 (4.3)*	–4.4 (5.9)*	–4.7 (4.7)*
Soft tissue swelling	0.3 (2.3)	–0.7 (1.6)	–1.2 (2.3)	–1.3 (1.3)*
Arthralgia	0.1 (1.8)	–0.3 (1.8)	–0.5 (2.5)	–0.4 (2.1)
Headache	0.1 (1.7)	–0.4 (1.6)	–0.3 (1.4)	–0.3 (2.0)
Perspiration	0.1 (1.7)	–0.6 (1.6)	–1.1 (1.3)*	–1.7 (1.6)*
Fatigue	0.7 (0.5)	–0.5 (1.4)*	–1.3 (1.7)*	–1.0 (1.6)*

Source: Somavert® Package Insert
Mean (SD)
* $p < 0.05$; see text for exact p-values

- Mean (± SD) ring size decreased from baseline (size "X" standard European jeweler's ring) to 12 weeks by 0.1 ± 2.3 size on placebo, by 0.8 ± 1.6 size on pegvisomant 10 mg ($p = 0.16$ vs. placebo), by 1.9 ± 2.0 sizes on pegvisomant 15 mg ($p = 0.001$), and by 2.5 ± 3.3 sizes on pegvisomant 20 mg ($p < 0.001$).

- Mean scores for individual signs and symptoms, and the mean total score increased slightly in the placebo group and decreased in all pegvisomant groups. Significant decreases were seen in the 20-mg pegvisomant group for soft tissue swelling ($p < 0.001$), the 15- and 20-mg pegvisomant groups for excessive perspiration ($p = 0.003$ and $p < 0.001$, respectively), and in all three pegvisomant groups for fatigue ($p = 0.03$ and $p < 0.001$ for 10 mg and both 15 and 20 mg, respectively), and total score ($p = 0.02$, $p = 0.004$, and $p < 0.001$ for 10, 15, and 20 mg, respectively).

- Serum GH concentrations increased and then leveled off in the pegvisomant groups in a dose-dependent fashion that coincided with the magnitude and timing of the reduction in IGF-1 (data were not shown in report).

- Serum GH concentrations at 12 weeks were significantly higher in the 15- and 20-mg pegvisomant groups than in the placebo group.

- Serum anti-GH antibodies 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).

- Mean tumor volume did not change significantly in any patient, nor did tumor volume change significantly more in any pegvisomant group compared with placebo.

Safety:

- Deaths and other serious adverse events: 1 patient was found to have

<table>
<tr><td></td><td>
increased ALT of 904 U/l (normal, 0 to 47) and AST of 389 U/l (normal, 0 to 37) after 8 weeks of treatment on pegvisomant 15 mg; patient withdrew from the study. Serum bilirubin and alkaline phosphatase did not increase, viral serologic tests were negative, and ultrasonography of the liver was normal. The serum enzyme values returned to normal within 8 weeks of discontinuation of pegvisomant. After rechallenge with 4 weeks of pegvisomant 10 mg/day, the enzymes increased again then returned to normal after drug discontinuation.

• Frequency of adverse events was similar in the pegvisomant and placebo groups, except for injection site reactions (see table below).

Adverse events that occurred in at least 10% of patients
<table>
<tr><th></th><th></th><th colspan="3">Pegvisomant (mg/d)</th></tr>
<tr><th></th><th>Placebo</th><th>10</th><th>15</th><th>20</th></tr>
<tr><th>Description</th><th>N = 32</th><th>N = 26</th><th>N = 26</th><th>N = 28</th></tr>
<tr><td>Upper respiratory tract infection</td><td>5 (16)</td><td>5 (19)</td><td>4 (15)</td><td>5 (18)</td></tr>
<tr><td>Headache</td><td>4 (12)</td><td>3 (12)</td><td>2 (8)</td><td>3 (11)</td></tr>
<tr><td>Injection-site reaction</td><td>0</td><td>2 (8)</td><td>1 (4)</td><td>3 (11)</td></tr>
<tr><td>Pain†</td><td>2 (6)</td><td>2 (8)</td><td>1 (4)</td><td>4 (14)</td></tr>
<tr><td>Diarrhea</td><td>1 (3)</td><td>1 (4)</td><td>0</td><td>4 (14)</td></tr>
<tr><td>Nausea</td><td>1 (3)</td><td>0</td><td>2 (8)</td><td>4 (14)</td></tr>
<tr><td>Flatulence</td><td>0</td><td>0</td><td>1 (4)</td><td>3 (11)</td></tr>
</table>
Values shown are number of patients (%); some patients had more than one adverse event.
† Included pain in the scalp, neck, shoulders, arms, and legs.

• Injection site reactions: characterized as mild, erythematous, self-limiting, and did not require treatment.
• Liver enzymes: except for the patient with the SAE, there were no significant increases in ALT or AST in any study group.
• Other laboratory tests: except for the patient with the SAE, changes in laboratory tests were small and clinically unimportant.
• Pegvisomant was well tolerated overall.
</td></tr>
<tr><td>Conclusions</td><td>Treatment of patients who have acromegaly with a growth hormone-receptor antagonist results in a reduction in serum IGF-1 concentrations and in clinical improvement. Longer treatment of more patients will be required before any conclusions can be drawn regarding the safety of the drug, including its effects on tumor size and hepatic function.</td></tr>
<tr><td>Critique</td><td>
• Strengths: well-designed, good-quality; results likely to apply to the VA population
• Limitations: efficacy analysis not ITT; no sample size or power calculation; confidence intervals not reported; short duration; studied mixed population with no efficacy analysis by patient subgroups according to prior treatment exposure
• Study support and disclosures: grant from Sensus Drug Development; authors have consulted for or obtained support, honorariums, or both from Sensus.
</td></tr>
</table>

Citation	**van der Lely AJ, Hutson RK, Trainer PJ et al. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 2001;358(9295):1754-9**
Study Goals	To evaluate the long-term safety and efficacy of pegvisomant
Methods	• **Study Design** ➢ Multinational (Germany, Netherlands, Sweden, UK, US), open-label, uncontrolled, observational, dose-titration study following placebo-controlled clinical trials (protocols SEN-3613A and SEN-3614/15) of daily pegvisomant therapy ➢ Somatostatin analogs and dopamine agonists were discontinued at the first screening visit ➢ Daily dosing of pegvisomant was started at 10 mg per day then titrated up or down as necessary by 5-mg per day to achieve a normal IGF-1 concentration or until a maximum of 40 mg per day; in protocol SEN-3614/15, intervals for dosage adjustments could not be less than 8 weeks apart ➢ Efficacy variables: IGF-1, GH, anti-GH antibodies, anti-pegvisomant antibodies (measured by a nonvalidated [?], semi-quantitative screening assay one month after treatment discontinuation to avoid cross-reactivity with pegvisomant), serum pegvisomant concentrations. ➢ Safety variables included alkaline phosphatase, ALT, AST, lactate dehydrogenase, total bilirubin, blood urea nitrogen, creatinine, cholesterol, triglycerides, hemoglobin, white blood cell count, platelet count, electrocardiogram, chest radiographs, vital signs, tumor volume by MRI, adverse events • **Data Analysis** ➢ Efficacy analysis included data from patients on daily pegvisomant dosing; 38 patients had received pegvisomant weekly (protocol SEN-3611/13) before being switched to daily dosing (SEN-3613A) ➢ For assessments of pegvisomant effects on IGF-1 and GH, patients were placed in cumulative cohorts depending on whether they had completed at least 6, 12, or 18 months of continuous daily pegvisomant therapy at the time of data cut-off ➢ Safety analysis included all data from patients exposed to pegvisomant during the clinical development program of the drug ➢ Assumption of normality of IGF-1, GH, insulin, glucose, and glycated hemoglobin data was investigated by using a Shapiro-Wilks test, in which the null hypothesis that the data represented a random sample from the normal distribution was rejected; Wilcoxon's signed rank test was used to assess the stastistical significance of changes from baseline for these measures
Criteria	• **Inclusion criteria** ➢ 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)

	• **Exclusion criteria** ➢ None stated
Results	• Exclusions from analysis: Of 167 patients who participated in the clinical development program, 7 received only placebo and are excluded from all analyses (total exposed: 160 patients). Another 3 patients received only a single dose of the drug, and 5 received only weekly doses; data from these 8 patients have been excluded from efficacy analyses (N = 152) but were included in safety analyses (N = 160). • Age 46 years; 94 males, 66 females; duration of disease 8 years; prior therapy: surgery 134 patients (84%), radiation 94 patients (59%), somatostatin analog 117 patients (73%); dopamine agonist 76 patients (48%). • Baseline differences: Mean serum IGF-1 and GH concentrations at baseline were higher for the 18-month cohort (N = 39) than for all exposed patients (N = 160); this difference was attributed to the more severe disease of patients entered in the earliest phase of clinical development. No other differences were noted. • Withdrawals: Overall, 30 (18.8%) of 160 exposed patients withdrew prematurely, 2 (1.2% of 160) for protocol violations, 5 (3.1%) because of lack of efficacy, 9 (5.6%) because of adverse events related to pegvisomant (including two with reversible increases in hepatic transaminases), 2 (1.2%) were lost to follow-up, and 12 were voluntary withdrawals. • Total exposure: 186 patient-years; mean duration of treatment, 425 days **Efficacy**: • The magnitude of decrease in IGF-1 concentrations at 12 and 18 months was similar to that seen with pegvisomant 20 mg/day in the 12-week placebo-controlled study by Trainer et al.[5] (See table below.)

Selected efficacy measures

	All exposed	Cohort on Daily Dosing			
	pts	All pts	6-mo	12-mo	18-mo
Variable	**N = 160**	**N = 152**	**N = 131**	**N = 90**	**N = 39**
Pegvisomant dose, mean ± SE (mg/d)	—	—	14.7 ± 0.4	18.0 ± 0.7	19.6 ± 1.4
IGF-1, mean ± SD (mcg/l)	762 ± 330	755 ± 327	760 ± 306	806 ± 297	847 ± 321
IGF-1 WNL, n (%)	—	—	—	87 (97%)	—
Baseline GH, mean ± SD (mcg/l)	10.2 ± 16.0	10.4 ± 16.3	10.9 ± 17.0	13.2 ± 19.7	19.2 ± 27.0
Change in GH (ng/ml)[§]	—	—	12.5 ± 2.1*	12.5 ± 3.1*	14.2 ± 5.7*
Tumor vol. (ml)	2.4 ± 3.4	2.4 ± 3.5	2.1 ± 2.5	2.4 ± 2.7	2.5 ± 2.6
Pegvisomant conc, mean ± SE (mg/l)	—	—	12.2 ± 0.7	17.6 ± 1.3	19.1 ± 2.8

WNL = Within age-adjusted normal limits
* $P < 0.05$ for within-cohort, baseline vs. final comparisons

	• 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. • Durability of response was assessed using the data from 38 patients treated daily with pegvisomant for a mean of 83 weeks. IGF-1 concentrations were within normal limits in 572 (91.7%) of 624 post-baseline visits. • Serum GH concentrations remained stable on pegvisomant for up to 18 months. • During a mean of 11.5 months of treatment, mean tumor volume was stable (with a change [± SE] of 0.033 ml ± 0.057 from 2.41 ml ± 0.31 at baseline to 2.37 ml ± 0.31 at final scan; p = 0.353). Tumor volumes decreased in 78 patients who had received radiotherapy (change from baseline of -0.126 ml ± 0.071 over 12.5 months; p = 0.214) and increased in 53 patients who had not received radiotherapy (change of 0.103 ml ± 0.093 over 10 months; p = 0.948). There was no association between the duration of pegvisomant therapy and change in tumor volume. • Anti-pegvisomant antibodies were detected in 27 (16.9%) of 160 patients 1 month after discontinuation of drug; 11 of the 27 patients had only single increases in titers ranging from 1:4 to 1:16. Persistent anti-pegvisomant antibodies were detected 1 to 2 months after stopping treatment in 10 (25.6%) of 39 patients, with titers ranging from 1:8 to 1:256. All of these patients also had anti-GH antibodies either during or after treatment. Normalization of IGF-1 was achieved in 9 of these patients and none showed evidence of tachyphylaxis. • Anti-GH antibodies were detected in 16 patients; 3 had sustained low titers and achieved normal IGF-1 within 2 months of starting treatment, and 13 patients had sporadically detected antibodies during the course of therapy. • Significant decreases (46%) in insulin concentrations were seen in the 12-month (p = 0.0075) and 18-month (p = 0.0393) cohorts. Fasting serum glucose decreased significantly from 1053 to 862 mg/l in the 6-month group (p = 0.013), and from 984 to 904 mg/l in the 18-month cohort (p = 0.0125). Glycated hemoglobin did not change significantly (data not shown here). **Safety**: • Deaths and other serious adverse events: Increased ALT and AST of more than ten times the upper limit of normal developed in two patients (1.2%) within 12 weeks of beginning pegvisomant. Both patients were withdrawn from the study. One patient is described in the summary of the study by Trainer et al. Both patients experienced mild fatigue and had normal biirubin concentrations. Liver transaminases returned to normal within several months after drug discontinuation. Two non-radiotherapy patients required surgery for rapid tumor growth, the cause of which was unclear. • Frequency of adverse events:

<table>
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The top five most frequent adverse events were infection, headache, pain, influenza-like syndrome, and accidental injury (see table).

Adverse events that occurred in at least 10% of patients
<table>
<tr><th>Description</th><th>n (%)</th></tr>
<tr><td>Infection</td><td>52 (33)</td></tr>
<tr><td>Headache</td><td>41 (26)</td></tr>
<tr><td>Pain</td><td>36 (23)</td></tr>
<tr><td>Influenza-like syndrome</td><td>33 (21)</td></tr>
<tr><td>Accidental injury</td><td>28 (18)</td></tr>
<tr><td>Diarrhea</td><td>23 (14)</td></tr>
<tr><td>Hypercholesterolemia</td><td>23 (14)</td></tr>
<tr><td>Back pain</td><td>21 (13)</td></tr>
<tr><td>Asthenia</td><td>21 (13)</td></tr>
<tr><td>Arthralgia</td><td>19 (12)</td></tr>
<tr><td>Injection site reaction</td><td>18 (11)</td></tr>
<tr><td>Sinusitis</td><td>16 (10)</td></tr>
</table>
N = 160

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.

• 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.

• Other biochemical test values remained within normal limits. No clinically relevant changes were seen in vital signs, electrocardiograms, or chest radiographs.
</td></tr>
<tr><td>Conclusions</td><td>Pegvisomant is an effective medical treatment for acromegaly.</td></tr>
<tr><td>Critique</td><td>
• Strengths: long-term evaluation of up to 18 months; assessed anti-pegvisomant antibodies; results probably applicable to VA patients

• Limitations: 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

• Study support and disclosures: Study was funded and designed by Sensus Drug Development Corporation
</td></tr>
</table>

Acquisition Costs

Average wholesale prices per vial of pegvisomant are about $90 for 10 mg, $135 for 15 mg, and $180 for 20 mg (according to Pfizer's AMCP-Formatted Formulary Submission Dossier, May 29, 2003). VA drug acquisition costs for pegvisomant are not listed since the drug is available only through the Bridge Program. A minimum 30-day supply of pegvisomant 10 mg is given at a price of $2812.

Cost Analysis

No published pharmacoeconomic studies of pegvisomant have been performed.

Data Compilation Table

IGF-1 WNL – PGV 20 mg s.c.	25/28 (89%)
IGF-1 WNL – PBO	3/31 (10%)
Treatment duration	12 weeks
Relative Risk	12%
Relative Risk Reduction (95% CI)	88% (65 to 96)
Absolute Risk	11%
Absolute Risk Reduction (95% CI)	79% (64 to 95)
NNT (95% CI)	1.2 (1 to 2)

PBO = Placebo; PGV = Pegvisomant

Three doses (10, 15, and 20 mg) of pegvisomant were compared in the placebo-controlled trial by Trainer et al.[5] A dose of 20 mg was selected for comparison here based on the mean dose required by patients treated for 18 months in the study by van der Lely.[6] This was the longest period studied and most likely to reflect prolonged dosing.

The NNT of 1.2 means 1 to 2 patients would need to be treated with pegvisomant rather than placebo for 12 weeks for one additional patient to achieve normalization of IGF-1.

Conclusion

Limited published data demonstrate that pegvisomant, the first growth hormone receptor antagonist to be developed, is a highly efficacious, novel agent for the treatment of acromegaly. Comparisons of IGF-1 normalization rates for pegvisomant and historical rates for somatostatin analogs suggest that pegvisomant is probably the most effective medical therapy available for acromegaly, either as a first- or second-line drug. Combined therapy with pegvisomant and somatostatin analogues in a selected subset of patients may be rational because of complementary mechanisms, but this clinical use is poorly documented. Pegvisomant is generally well tolerated but may be hepatotoxic. In addition, its long-term safety, particularly with regard to liver toxicity, immunogenicity and stimulation of tumor growth, are uncertain. The only distribution channel for the drug is directly to the patient through Pfizer's Bridge Program.

Recommendations

Based on the clinical review, pegvisoment is highly efficacious for acromegaly, but the drug may be hepatotoxic and more long-term experience with the drug is needed. It should be reserved for second-line drug therapy in patients who have had an inadequate response to or are not appropriate candidates for surgery and/or radiation therapy, and who also have had an inadequate response to maximal doses of somatostatin analogs with or without dopamine agonists, or who have documented intolerance or hypersensitivity to somatostatin analogs. Combination therapy with pegvisomant and somatostatin analogs is usually not necessary but may be rational in patients who meet the above criteria and also have rapidly growing tumors. In this subset of patients, the somatostatin analog may prevent tumor growth while pegvisomant normalizes serum IGF-1 concentrations.

The drug should remain nonformulary at the national and VISN levels.

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