

London, 19 January 2012  
EMA/271972/2012  
Human Medicines Development and Evaluation

**WITHDRAWAL ASSESSMENT REPORT  
FOR  
SOMAVERT**

International Nonproprietary Name:  
pegvisomant

**Procedure No. EMEA/H/C/409/X/0052**

This withdrawal Assessment Report is based on the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the application, with all information of a commercially confidential nature deleted. It may not include all available information on the product in the event that the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application. It should therefore be read in conjunction with the "Questions and Answers" document on the withdrawal of the application, which provides an overview of all available information at the time of the Applicant's withdrawal.

# 1. CHMP RECOMMENDATION PRIOR TO THE WITHDRAWAL

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Somavert 25 mg powder and solvent for solution for injection and Somavert 30 mg powder and solvent for solution for injection in the treatment of acromegaly:

- **is not approvable** since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the CHMP list of questions.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

## Quality

The validation and stability data for the new presentations applied for, i.e. Somavert 25 mg powder and solvent for solution for injection and Somavert 30 mg powder and solvent for solution for injection, were not provided.

## Safety

In study A6291026, the bioavailability of the proposed 30 mg presentation is 123.89% (90% CI 112.91 – 135.93) that of 2 injections of the 15 mg presentation. The potential clinical consequences, especially in terms of safety aspects, of switching to a formulation showing on average 25% greater bioavailability should be further discussed by the Applicant.

## Proposal for Questions to be posed to additional Experts

At present there are no questions to be posed to additional Experts.

## Proposal for Inspection

There is no proposal for inspection.

# 2. EXECUTIVE SUMMARY

## *Problem statement*

This new marketing authorisation application for Somavert 25 mg powder and solvent for solution for injection and Somavert 30 mg powder and solvent for solution for injection was submitted as an extension application (Annex II of Commission Regulation (EC) 1085/2003) following the application for a "Biological Medicinal Product" under Article 8(3) of Directive 2001/83/EC (as amended) for Somavert 10 mg, 15 mg and 20 mg powder and solvent for solution for injection (powder and s.f.s.f.i), EMEA/H/C/409, which was approved by the European Commission on 13 November 2002.

Pegvisomant is a recombinant protein of human DNA origin in which human growth hormone (GH) has been mutated to alter its binding characteristics to the human GH receptor (GHR). The purpose for adding the PEG moieties to compound B2036 is to increase the biological half-life and to reduce the likelihood of antibody formation. The pharmacologic effect of pegvisomant is a result of its reversible binding to the growth hormone receptor. This reversible binding will lead to blocking of signal transduction and to reductions in circulating insulin-like growth factor I (IGF-I).

Somavert is used to treat patients with acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, which is caused by the pituitary gland producing excess growth hormone. Somavert is used in patients who did not respond well to surgery or radiation therapy, or to treatment with somatostatin analogues.

All indications which have previously been approved for the reference product Somavert 15 mg powder and s.f.s.f.i (EMA/H/C/409) are claimed for Somavert 25 mg and 30 mg powder and s.f.s.f.i.:

“Treatment of adult patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-I concentrations or was not tolerated”.

### ***About the product***

Currently registered strengths are:

- Somavert 10 mg powder and solvent for solution for injection
- Somavert 15 mg powder and solvent for solution for injection
- Somavert 20 mg powder and solvent for solution for injection

This application concerns two new strengths:

- Somavert 25 mg powder and solvent for solution for injection
- Somavert 30 mg powder and solvent for solution for injection

### ***The development programme/Compliance with CHMP Guidance/Scientific Advice***

No Scientific Advice was received for these applications.

### ***General comments on compliance with GMP, GLP, GCP***

According to the company all studies were performed with respect to the GCP guidelines.

### ***Type of application and other comments on the submitted dossier***

- *Legal basis*

This new marketing authorisation application for Somavert 25 mg powder and solvent for solution for injection and Somavert 30 mg powder and solvent for solution for injection is submitted as an extension application (Annex II of Commission Regulation (EC) 1085/2003) following the application for a “Biological Medicinal Product” under Article 8(3) of Directive 2001/83/EC (as amended) for Somavert 10 mg, 15 mg and 20 mg powder and solvent for solution for injection (powder and s.f.s.f.i), EMEA/H/C/409, which was approved by the European Commission on 13 November 2002.

Since the product is manufactured using recombinant DNA technology the centralised procedure is mandatory.

In support of the current application, pharmacokinetic (PK) data were obtained from one unique Pharmacokinetic Study [A6291026](#). In this open-label, phase I, single-dose, cross-over study, pharmacokinetics of Somavert 15 mg powder and s.f.s.f.i Somavert 30 mg powder and s.f.s.f.i were compared. No new clinical efficacy data were submitted. Pharmacokinetic data are considered *a priori* sufficient to extrapolate the efficacy and the safety of the already registered 15 mg powder and solvent for solution for injection to the newly proposed dosages 25 mg and 30 mg.

### 3. SCIENTIFIC OVERVIEW AND DISCUSSION

#### *Introduction*

In support of the current application, pharmacokinetic (PK) data were obtained from one unique Pharmacokinetic Study [A6291026](#). In this open-label, phase I, single-dose, cross-over study, pharmacokinetics of Somavert 15 mg powder and s.f.s.f.i Somavert 30 mg powder and s.f.s.f.i were compared. No new clinical efficacy data were submitted. Pharmacokinetic data are considered *a priori* sufficient to extrapolate the efficacy and the safety of the already registered 15 mg powder and solvent for solution for injection to the newly proposed dosages 25 mg and 30 mg.

#### *Quality aspects*

- **Drug substance**

The manufacturing process of the drug substance (pegvisomant) is not impacted by addition of the 25mg and 30 mg strengths. A summary of the facilities and their responsibilities for manufacture and testing of Pegvisomant is provided in the documentation. No other documentation is provided for the drug substance.

- **Drug Product**

Currently, the medicinal product is supplied in single-dose vials containing 10, 15, or 20 mg of pegvisomant as a sterile, white lyophilized powder intended for subcutaneous injection after reconstitution with 1 mL of sterile water for injection. The Marketing Authorisation Holder (MAH) seeks approval for two additional new strengths, 25 mg and 30 mg presentations of pegvisomant. Apart from development data obtained at pilot scale, no validation data was provided. The applicant intends to qualify the manufacture of 25mg and 30mg strengths at full scale in the future, for the filling and the lyophilization steps.

Specifications at release and at shelf-life remain the same for all the strengths, except for the strength. Batch analyses are provided for only for two 25mg/vial pilot-scale batches and one 30 mg/vial clinical batches, however, these may only be considered as supportive of the future commercial batches for which analytical results should have been provided.

No modification is introduced for the container closure system.

Stability study was initiated, and will performed for up to 36 months at 2-8°C, 25°C/60%RH, and 40°C/75%RH for 4 pilot-scale batches (2 batches of 25mg/vial and 2 batches of 30 mg/vial),.and 6 months stability data are available. All the stability data are within the acceptance criteria. A slight increase in the moisture content is observed for both strengths.

No stability data has been provided for the final commercial process of the 2 requested strengths.

- **Conclusions on the chemical, pharmaceutical and biological aspects**

In the absence of validation and stability data this extension application is not recommended for approval.

#### *Non clinical aspects*

No new non clinical data were submitted for this application.

In 2009, a variation (EMA/H/C/409/II/35) was submitted to update the SmPC following the completion of a carcinogenicity study in rat. It was concluded that malignant fibrous histiocytomas associated with fibrosis and histiocytic inflammation were observed at injection sites in males in the rat carcinogenicity study at exposure levels equivalent to three times the human exposure based on mean plasma concentrations in two long-term studies at a daily dose of 30 mg. The relevance of this response for humans is currently unknown.

The non clinical data that supported the Marketing Authorizations for the approved strengths also support the current application.

## Clinical aspects

### • Tabular overview of clinical studies

Phase	Study	Design	Treatment duration	Treatment groups
I	Study A 6291026	Open-label Crossover	Single-dose	Reference: <b>Somavert 2 x 15 mg</b> Test: <b>Somavert 30 mg</b>

### Pharmacokinetics

In support of the current application, pharmacokinetic (PK) data were obtained from one unique Pharmacokinetic Study [A6291026](#). In this open-label, phase I, single-dose, cross-over study, pharmacokinetics of Somavert 15 mg powder and s.f.s.f.i Somavert 30 mg powder and s.f.s.f.i were compared.

In this study, the relative bioavailability of 1 x 30 mg/ml versus 2 x 15 mg/ml administration was 123.89% (90% confidence interval 112.9% - 135.93%). See Table 1.

**Table 1 Statistical summary of treatment comparisons for serum pegvisomant parameters: 1 X 30 mg/ml versus 2 X 15 mg/ml**

n = 14	Pegvisomant Test : 30 mg	Pegvisomant Reference : 2x15 mg	F-ANOVA p, CVres %	GMR CI 90%
AUC <sub>t</sub> h $\times$ $\mu$ g/ml	210.1 $\pm$ 117.1 CV = 56%	168.2 $\pm$ 94.1 CV = 56 %	F = 16.24 p = 0.0017 CV = 14.9%	125.38 [113.45 – 138.58]
AUC $\infty$ h $\times$ $\mu$ g/ml	215.3 $\pm$ 116.1 CV = 54 %	173.8 $\pm$ 92.9 CV = 53 %	F = 16.94 p = 0.0014 CV = 13.8%	123.89 [112.91 – 135.93]
C <sub>max</sub> ng/ml	1843 $\pm$ 1035.5 CV = 56 %	1791 $\pm$ 1027.5 CV = 57 %	F = 0.80 P = 0.3893 CV = 15.8%	105.46 [94.85 – 117.25]
T <sub>max</sub> H	Median : 54.1 (36 – 84 h)	Median : 42.0 (30 – 84 h)	•	•
T <sub>1/2</sub> , h	59.84 $\pm$ 13.02	64.06 $\pm$ 19.26		

AUC $\infty$ , AUC<sub>t</sub>, C<sub>max</sub> = arithmetic mean  $\pm$  SD - IC90% after log transformation

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Possible causes of this bioavailability difference were explored by the Applicant. Review of the laboratory/ manufacturing documents revealed that the actual pegvisomant doses in the 30 mg-vial and in the 15 mg-mg vial were different from their nominal values: 32 mg in the 30 mg-vial and 14.6 mg in the 15 mg-vial. Relative bioavailability, estimated by the ratio of the dose adjusted AUCinf was 112.97% with a 90% CI of 103.09-123.80%.

From a regulatory point of view, we are not ready to accept such dose-normalisation because:

- The Applicant has not documented that such difference in assay content is always the case in more than one single batch;
- When content correction is to be used, this should be pre-specified in the protocol.

However, since Study A6291026 is not a bioequivalence study comparing a new product from a generic company to a reference product of an innovator, we may accept wider acceptance range than 80.00% – 125.00% to conclude bioequivalence between the new 30 mg formulation and the already authorised 15 mg formulation (given as 2 sequential injections). But before drawing any conclusion, the potential clinical consequences of switching on a presentation showing on average 25% greater bioavailability should be discussed by the Applicant.

In order to provide precise guidance to prescribers, the Applicant proposed to add the following sentences in the SmPC:

- **Section 4.2 Posology and method of administration:** *"IGF-I levels should be monitored when doses are adjusted, including conversion from administration of multiple daily injections, as combinations of 10, 15 and 20 mg vials, to a single daily injection of the same total dose of 25 mg or 30 mg (see section 5.2)";*
- **Section 5.2 Pharmacokinetic properties:** *"Administration of a single injection using a 30 mg vial yielded a mean 24% (90% CI: 13-36%) higher AUC compared to the equivalent dose administered as two separate injections from two 15 mg vials".*

## Pharmacodynamics

No new pharmacodynamic data were submitted. This is acceptable as the active substance is the same as for the already approved Somavert 10 mg, 15 mg and 20 mg powder and solvent for solution for injection.

## Conclusions on clinical pharmacology

The active compound of Somavert, pegvisomant, has been evaluated by the CHMP before and has been approved since November 2002 in the treatment of acromegaly in patients who did not respond well to surgery or radiation therapy, or to treatment with somatostatin analogues. Somavert is designed an "orphan medicine" drug.

Pegvisomant is supplied in vials as a sterile, white lyophilized powder intended for subcutaneous injection after reconstitution with 1 mL of sterile water for injection. The product is currently available in single-dose sterile vials containing 10, 15, or 20 mg of pegvisomant. As maintenance doses of up to 30 mg daily have been approved, the new presentations Somavert 25 mg powder and solvent for solution for injection and Somavert 30 mg powder and solvent for solution for injection will simplify drug administration by reducing the number of injections for patients who require doses greater than 20 mg to control IGF-I levels.

Study A6291026 showed that the bioavailability of the proposed 30 mg presentation was 123.89 % that of 2 injections of the 15 mg presentation. Therefore, the submitted pharmacokinetic study is sufficient to extrapolate the effectiveness of the already registered 15 mg powder and solvent for solution for injection to the newly proposed dosages 25 mg and 30 mg.

In clinical practice, the safety margin of the product is rather high as loading doses of 80 mg are administered at the beginning of the treatment. According to the current SmPC, there is limited experience of overdose with SOMAVERT. In the one reported incident of acute overdose, where 80 mg/day was administered for 7 days, the patient experienced a slight increase in fatigue and dry mouth. In the week following discontinuation of treatment the adverse reactions noted were: insomnia,

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increased fatigue, oedema peripheral, tremor, and weight gain. But the potential clinical consequences of switching on a formulation showing on average 25% greater bioavailability in terms of safety aspects are unknown and the safety data from the single-dose pharmacokinetic study A6291026 in healthy subjects could not permit to address this question. In particular, patients switching from 2 injections of the 15 mg presentation could be exposed to higher doses of pegvisomant during a substantial period.

In this respect, the Applicant proposed to add in Section 4.2 of the SmPC that IGF-1 levels should be systematically measured when doses are adjusted, including when switching from multiple daily injections (using the 10, 15 or 20 mg vials) to a single daily injection (using the 25 or 30 mg vials). From our point of view, this recommendation is confusing and could not be endorsed, as two situations should be considered separately:

- first, an increase of the dose based on IGF-1 levels. This is already covered in Section 4.2 of the SmPC: "Serum IGF-1 levels should be measured every four to six weeks and appropriate dose adjustments made to maintain the serum IGF-1 levels within the age-adjusted normal range" and no justification was submitted by the Applicant to support the need for additional IGF-1 measurements.

- second, a switch from multiple daily injections (using the 10, 15 or 20 mg vials) to a single daily injection (using the 25 or 30 mg vials), that is to say the treatment continues with same dose. The clinical consequences of an average 25% greater bioavailability with the 30 mg formulation when compared to two injections of the 15 mg formulation are unknown, therefore it is unclear on which basis the Applicant recommend to measure IGF-1 levels in this case. For this reason, the cross-reference to the results of study A6291026 in Section 5.2 could not be endorsed. Moreover, it is not clear in which delay IGF-1 levels should be measured again and why the current recommendation to measure IGF-1 levels every four to six weeks could not apply here.

## **Clinical efficacy**

No new clinical efficacy data were submitted. Study A6291026 showed that the bioavailability of the proposed 30 mg presentation was 123.89% that of 2 injections of the 15 mg presentation. Therefore, the submitted pharmacokinetic study is sufficient to extrapolate the effectiveness of the already registered 15 mg powder and solvent for solution for injection to the newly proposed dosages 25 mg and 30 mg.

## **Clinical safety**

### ***Patient exposure***

For the new presentation 30 mg/vial, the safety set is constituted of 14 subjects participating to study A 6291026.

### ***Adverse events***

The number of AEs was similar for both treatments: 7 subjects reported a total of 8 AEs after administration of 2 x 15 mg/mL pegvisomant, and 4 subjects reported a total of 7 AEs after administration of 1 x 30 mg/mL pegvisomant. Except for 1 reported AE of moderate severity (musculoskeletal chest pain after 2 x 15 mg/mL pegvisomant), all AEs were of mild severity. All AEs had resolved at the end of the study, except for 1 case of 'transaminases increased' after 2 x 15 mg/mL pegvisomant that resolved spontaneously at further follow-up.

On a system-organ class (SOC) level, only Gastrointestinal Disorders (diarrhoea and vomiting), and Respiratory, Thoracic and Mediastinal Disorders (nasal congestion and rhinorrhoea) were observed in more than 1 subject per treatment (2 subjects for each SOC).



MedDRA (v13.1) System Organ Class Preferred Term	Number of subjects with adverse events All causality (treatment-related)	
	2 x 15 mg/mL Pegvisomant	1 x 30 mg/mL Pegvisomant
<b>Gastrointestinal disorders</b>	<b>2 (2)</b>	<b>1 (1)</b>
Abdominal pain upper	0 (0)	1 (1)
Diarrhoea	1 (1)	0 (0)
Vomiting	1 (1)	0 (0)
<b>General disorders and administration site conditions</b>	<b>1 (0)</b>	<b>1 (0)</b>
Catheter site pain	1 (0)	1 (0)
<b>Injury, poisoning and procedural complications</b>	<b>1 (0)</b>	<b>1 (0)</b>
Arthropod bite	1 (0)	1 (0)
<b>Investigations<sup>a</sup></b>	<b>1 (0*)</b>	<b>0 (0)</b>
Transaminases increased <sup>a</sup>	1 (0*)	0 (0)
<b>Musculoskeletal and connective tissue disorders</b>	<b>1 (1)</b>	<b>1 (1)</b>
Musculoskeletal chest pain	1 (1)	1 (1)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>1 (1)</b>	<b>2 (2)</b>
Nasal congestion	0 (0)	1 (1)
Rhinorrhoea	1 (1)	1 (1)
<b>Skin and subcutaneous tissue disorders</b>	<b>1 (1)</b>	<b>1 (1)</b>
Acne	1 (1)	1 (1)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PIMS = Phase 1 Management System

\*The AE 'transaminases increased' was erroneously recorded as being not related to treatment in the PIMS source database, whereas it should have been recorded as being treatment-related. Therefore, the numbers in between brackets should actually have read 1 instead of 0. See CSR errata.

#### ***Serious adverse events and deaths***

There were no deaths or SAEs reported in this study.

#### ***Laboratory findings***

No significant laboratory findings were reported. Only three laboratory abnormalities were reported, none of these abnormalities were reported as AEs.

#### ***Safety in special populations***

N/A

#### ***Immunological events***

Itching, redness, swelling, or ulceration at the injection site were not observed. Pain of mild severity was reported after treatment with 2 x 15 mg/mL pegvisomant for 2 subjects.

Fullness in the abdominal wall of mild severity was reported after treatment with 2 x 15 mg/mL pegvisomant for 1 subject and after treatment with 1 x 30 mg/mL pegvisomant for another subject. None of the injection site reactions were clinically significant or reported as AE.

#### ***Safety related to drug-drug interactions and other interactions***

N/A

#### ***Discontinuation due to AES***

There were no discontinuations reported in this study.

## **Conclusions on clinical safety**

The safety profile of pegvisomant in the treatment of acromegaly is well known. The most common side effects of Somavert during the clinical study were injection site reactions (seen in 11% of the patients), sweating (7%), headache (6%) and asthenia (loss of strength and energy, 6%). Some patients who received Somavert developed anti-growth hormone antibodies (proteins that are produced in response to Somavert). The limited safety data from the pharmacokinetic study A6291026



submitted for this extension application did not reveal unexpected adverse events compared to the already authorized presentations. The local tolerance at the injection site with the 30 mg new formulation was good.

However, study A6291026 showed that the bioavailability of the proposed 30 mg presentation was 123.89% that of 2 injections of the 15 mg presentation. In clinical practice, the safety margin of the product is rather high as loading doses of 80 mg are administered at the beginning of the treatment. But the potential clinical consequences for patients of switching on a formulation showing on average 25% greater bioavailability in terms of safety aspects is unknown and the safety data from the single-dose pharmacokinetic study A6291026 in healthy subjects could not permit to address this question. The Applicant should further discuss.

## **Pharmacovigilance system**

A Detailed Description of the Pharmacovigilance System (DDPS) dated November 2010 (version 3.0) has been submitted by the Applicant.

## **Risk Management plan**

- No Risk Management Plan was submitted for this extension application.
- No Risk Management Plan was submitted at the time of the authorisation of Somavert 10 mg, 15 mg and 20 mg powder and solvent for solution for injection.

## **ORPHAN MEDICINAL PRODUCTS**

This medicine has an "orphan designation" which means that it is used to treat life-threatening or chronically debilitating conditions that affect no more than five in 10,000 people in the European Union, or are medicines which, for economic reasons, would be unlikely to be developed without incentives.

# **4. BENEFIT RISK ASSESSMENT**

## **Benefits**

### ***Beneficial effects***

The active compound of Somavert, pegvisomant, has been evaluated by the CHMP before and has been approved since November 2002 in the treatment of acromegaly in patients who did not adequately respond to surgery or radiation therapy, or to treatment with somatostatin analogues. Somavert is designed an "orphan medicine" drug.

Pegvisomant is supplied in vials as a sterile, white lyophilized powder intended for subcutaneous injection after reconstitution with 1 mL of sterile water for injection. The product is currently available in single-dose sterile vials containing 10, 15, or 20 mg of pegvisomant. As maintenance doses of up to 30 mg daily have been approved, the new presentations Somavert 25 mg powder and solvent for solution for injection and Somavert 30 mg powder and solvent for solution for injection will simplify drug administration by reducing the number of injections for patients who require doses greater than 20 mg to control IGF-I levels.

Study A6291026 showed that the bioavailability of the proposed 30 mg presentation was 123.89% that of 2 injections of the 15 mg presentation. Therefore, the submitted pharmacokinetic study is sufficient to extrapolate the effectiveness of the already registered 15 mg powder and solvent for solution for injection to the newly proposed dosages 25 mg and 30 mg. In clinical practice, dose adjustments should be made based on serum IGF-1 levels measured every four to six weeks, to maintain an optimal therapeutic response.

### ***Uncertainty in the knowledge about the beneficial effects***

None.

## Risks

### *Unfavourable effects*

The safety profile of pegvisomant in the treatment of acromegaly is well known. The most common side effects of Somavert during the clinical study were injection site reactions (seen in 11% of the patients), sweating (7%), headache (6%) and asthenia (loss of strength and energy, 6%). Some patients who received Somavert developed anti-growth hormone antibodies.

The limited safety data from the pharmacokinetic study A6291026 submitted for this extension application did not reveal unexpected adverse events compared to the already authorized presentations. The local tolerance at the injection site with the 30 mg new formulation was good.

### *Uncertainty in the knowledge about the unfavourable effects*

Study A6291026 showed that the bioavailability of the proposed 30 mg presentation was 123.89% that of 2 injections of the 15 mg presentation. In clinical practice, the safety margin of the product is rather high as loading doses of 80 mg are administered at the beginning of the treatment. According to the current SmPC, there is limited experience of overdose with SOMAVERT. In the one reported incident of acute overdose, where 80 mg/day was administered for 7 days, the patient experienced slight increase in fatigue and dry mouth. In the week following discontinuation, the adverse reactions noted were: insomnia, increased fatigue, oedema peripheral, tremor, and weight gain. However, the potential, especially long term, clinical consequences of switching on a formulation showing on average 25% greater bioavailability in terms of safety aspects are unknown and the safety data from the single-dose pharmacokinetic study A6291026 in healthy subjects could not permit addressing this question. In particular, patients switching from 2 injections of the 15 mg presentation could be exposed to higher doses of pegvisomant during a substantial period of time. The Applicant should further discuss this issue.

The Applicant also proposed to add in the SmPC that IGF-1 levels should be systematically measured when switching from multiple daily injections (using the 10, 15 or 20 mg vials) to a single daily injection (using the 25 or 30 mg vials). However, no sound rationale is submitted to support this proposal and it is unclear if this recommendation is for safety or efficacy purposes. Thus, the Applicant should further justify why the current recommendation to measure IGF-1 levels every four to six weeks is not sufficient when switching from multiple daily injections to a single daily injection.

## Balance

### *Importance of favourable and unfavourable effects*

Study A6291026 showed that the bioavailability of the proposed 30 mg presentation was 123.89% that of 2 injections of the 15 mg presentation. Therefore, the submitted pharmacokinetic study is sufficient to extrapolate the effectiveness of the already registered 15 mg powder and solvent for solution for injection to the newly proposed dosages 25 mg and 30 mg. As maintenance doses of up to 30 mg daily have been approved, the new presentations Somavert 25 mg and Somavert 30 mg, powder and solvent for solution for injection will simplify drug administration by reducing the number of injections for patients who require doses greater than 20 mg to control IGF-I levels.

However, the potential clinical consequences of switching on a formulation showing on average 25% greater bioavailability in terms of safety aspects is unknown and should be further discussed by the Applicant. In particular, patients switching from 2 injections of the 15 mg presentation could be exposed to higher doses of pegvisomant during a substantial period of time.

## Benefit-risk balance

At this step of the procedure, the overall B/R of Somavert 25 mg, powder and solvent for solution for injection and Somavert 30 mg, powder and solvent for solution for injection is negative as validation and stability data for the new presentations applied for, i.e. Somavert 25 mg powder and solvent for solution for injection and Somavert 30 mg powder and solvent for solution for injection, were not provided.

## **5. CONCLUSIONS**

At this step of the procedure, the overall B/R of Somavert 25 mg, powder and solvent for solution for injection and Somavert 30 mg, powder and solvent for solution for injection is negative as there is a quality and a safety major objection.