PRODUCT INFORMATION

SOMAVERT® pegvisomant (rbe)

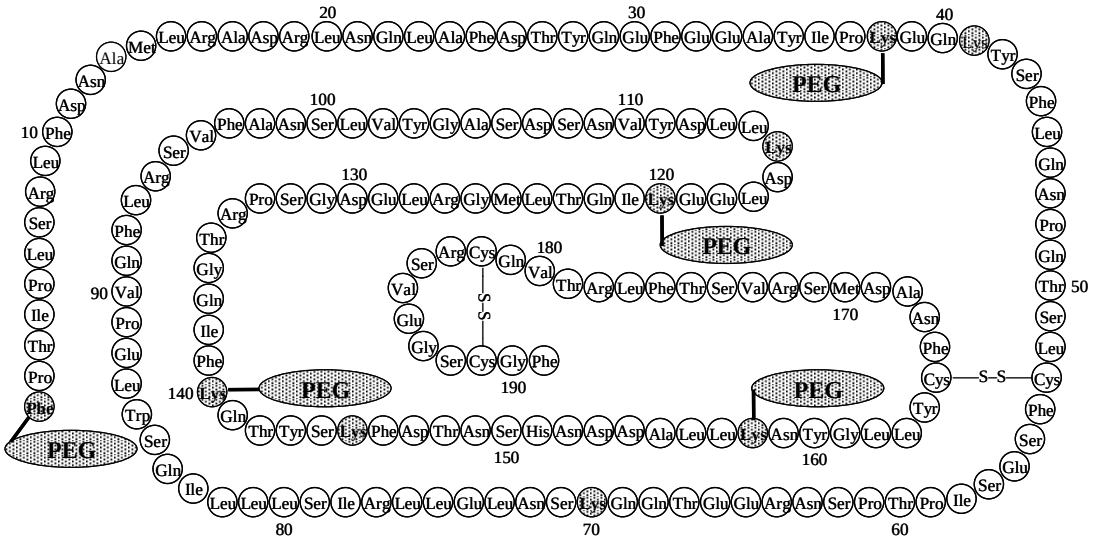
NAME OF THE MEDICINE

SOMAVERT (pegvisomant, rbe) Powder for Injection with Diluent 10 mg, 15 mg and 20 mg.

Pegvisomant is an analogue of human growth hormone (GH) that has been structurally altered to act as a GH receptor antagonist.

Pegvisomant is a protein of recombinant DNA origin containing 191 amino acid residues to which several polyethylene glycol (PEG) polymers are covalently bound (predominantly 4 to 6 PEG/protein molecule). The molecular weight of the protein of pegvisomant is 21,998 Daltons. The molecular weight of the PEG portion of pegvisomant is approximately 5000 Daltons. The predominant molecular weights of pegvisomant are thus approximately 42,000, 47,000 and 52,000 Daltons. The schematic below shows the amino acid sequence of the pegvisomant protein (PEG polymers are shown attached to the 5 most probable attachment sites). Pegvisomant is synthesised by a specific strain of *Escherichia coli* bacteria that has been genetically modified by the addition of a plasmid that carries a gene for GH receptor antagonist. Biological potency is determined using a cell proliferation bioassay.

Amino Acid Sequence of Pegvisomant Protein



PEG attachment sites: Phe_1, Lys_{38}, Lys_{41}, Lys_{70}, Lys_{115}, Lys_{120}, Lys_{140}, Lys_{145}, Lys_{158}

CAS No: 218620-50-9

DESCRIPTION

SOMAVERT is supplied as a sterile, white lyophilised powder intended for subcutaneous injection after reconstitution with 1 mL of sterile Water for Injections. SOMAVERT is available in single-dose sterile vials containing 10, 15, or 20 mg of pegvisomant protein (approximately 10, 15, and 20 U activity, respectively). Vials containing 10, 15, and 20 mg of pegvisomant protein correspond to approximately 21, 32, and 43 mg pegvisomant, respectively. Each vial also contains 1.36 mg of glycine, 36.0 mg of mannitol, 1.04 mg of dibasic sodium phosphate, and 0.36 mg of sodium phosphate - monobasic monohydrate.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: ATC code: H01AX01

Pegvisomant is an analogue of human growth hormone that has been genetically modified to be a growth hormone receptor antagonist.

Pegvisomant binds to growth hormone receptors on cell surfaces, where it blocks the binding of endogenous growth hormone, and thus interferes with intracellular growth hormone signal transduction. Limited *in vitro* studies suggest that pegvisomant does not bind to other cytokine receptors, including prolactin. Inhibition of growth hormone action with pegvisomant leads to decreased serum concentrations of insulin-like growth factor-I (IGF-I), as well as other growth hormone-responsive serum proteins such as free IGF-I, the acid-labile subunit of IGF-I (ALS), and insulin-like growth factor binding protein-3 (IGFBP-3).

Pharmacokinetics

Absorption:

Absorption of pegvisomant following subcutaneous administration is slow and prolonged, and peak serum pegvisomant concentrations are not generally attained until 33-77 hours after administration. The mean extent of absorption of a 20 mg subcutaneous dose was 57%, relative to a 10 mg intravenous dose.

Distribution:

The mean apparent volume of distribution of pegvisomant is relatively small (7 L, with a coefficient of variation of 12%).

After single subcutaneous pegvisomant administration no linearity is observed with rising doses of 10, 15 or 20 mg. Approximately linear pharmacokinetics are observed at steady state in the population pharmacokinetic studies. Mean ± SEM serum pegvisomant concentrations after 12 weeks of therapy with daily doses of 10, 15, and 20 mg were 6600 ± 1330; 16,000 ± 2200; and 27,000 ± 3100 ng/mL, respectively.

Metabolism and Elimination:

The pegvisomant molecule contains covalently bound polyethylene glycol polymers in order to reduce the clearance rate. Clearance of pegvisomant following multiple doses is lower than seen following a single dose. The mean total body systemic clearance of pegvisomant following multiple doses is estimated to be 28 mL/h for subcutaneous doses ranging from 10 to 20 mg/day. Clearance of pegvisomant was found to increase with body weight. Pegvisomant is slowly eliminated from serum, with a mean half-life of approximately 6 days (138 hours) following either single or multiple doses. Renal clearance of pegvisomant is negligible and accounts for less than 1% of total body clearance. The elimination route of pegvisomant has not been studied in humans.

The pharmacokinetics of pegvisomant are similar in normal healthy volunteers and acromegaly patients. Heavier individuals tend to have a higher total body clearance of pegvisomant than lighter individuals, and may thus require greater doses of pegvisomant.

Special Populations:

No pharmacokinetic data in special populations (children, elderly, populations with renal or hepatic impairment) are available.

The effect of race on the pharmacokinetics of pegvisomant has not been studied.

No gender effect on the pharmacokinetics of pegvisomant was found in a population pharmacokinetic analysis.

CLINICAL TRIALS

Acromegalic patients (n=112) previously treated with surgery, radiation therapy and/or medical therapies participated in a 12-week, randomised, double-blind, multicentre study comparing placebo and SOMAVERT. Following withdrawal from previous medical therapy, the 80 patients randomised to treatment with SOMAVERT received an 80 mg subcutaneous (SC) loading dose, followed by 10, 15 or 20 mg/day SC. Dose dependent, statistically significant reductions in mean IGF-I ($p< 0.0001$), free IGF-I ($p<0.05$), IGFBP-3 ($p<0.05$) and ALS ($p<0.05$) were observed at all post-baseline visits in the SOMAVERT treatment groups (see Figure 1 and Table 1).

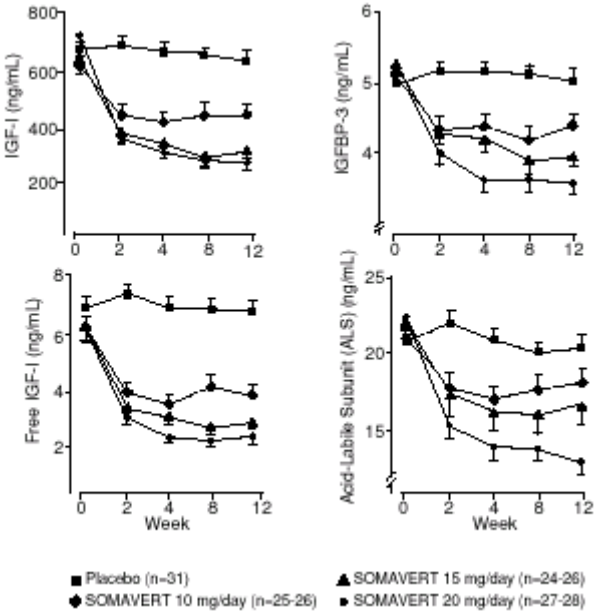


Figure 1. Effects of SOMAVERT on Serum Markers (Mean ± Standard Error)

Table 1. Mean Percent Change from Baseline in IGF-I at Week 12 for Intent-to-Treat Population

	SOMAVERT			Placebo n=31
	10 mg/day n=26	15 mg/day n=26	20 mg/day n=28	
Mean percent change from baseline in IGF-I (SD)	-27 (28)	-48 (26)	-63 (21)	-4.0 (17)
SOMAVERT minus Placebo (95% CI for treatment difference)	-23† (-35, -11)	-44† (-56, -33)	-59† (-68, -49)	

†P<0.01

Serum IGF-I levels were normalised at the end of the study (week 12) in 9.7%, 38.5%, 75% and 82% of subjects treated with placebo, 10 mg/day, 15 mg/day or 20 mg/day SOMAVERT respectively.

Statistically significant differences from placebo ($p<0.05$) were observed for improvements in the total signs and symptoms score for all dose groups compared to placebo.

A cohort of 38 acromegalic subjects has been followed in a long-term, open-label, dose-titration study for at least 19 consecutive months of daily dosing with SOMAVERT (mean = 84.7 weeks). The mean IGF-I concentration in this cohort fell from 917 ng/mL to 303 ng/mL on SOMAVERT, with 94.7% achieving a normal (age-adjusted) IGF-I concentration. After the first visit at which a normal IGF-I concentration was observed, IGF-I levels remained within the normal range over a mean duration of 19 consecutive months.

INDICATIONS

The treatment of acromegaly in patients who have had inadequate response to surgery and/or radiation and/or other medical therapies or for whom these therapies are not appropriate. The treatment goal is to normalise IGF-I levels.

CONTRAINDICATIONS

SOMAVERT is contraindicated in patients with a history of hypersensitivity to pegvisomant or any of the excipients.

PRECAUTIONS

Tumour Growth

Growth hormone-secreting pituitary tumours may sometimes expand, causing serious complications (for example, visual field defects).

Treatment by SOMAVERT does not reduce tumour size. Therefore, all patients with these tumours should be carefully monitored in order to detect any potential progression in tumour size.

During clinical studies with SOMAVERT, two patients manifested progressive tumour growth. Both patients had, at baseline, large globular tumours impinging on the optic chiasm, which had been relatively resistant to previous anti-acromegalic therapies. Overall, mean tumour size was unchanged during the course of treatment with SOMAVERT in the clinical studies.

Glucose Metabolism

Growth hormone opposes the effects of insulin on carbohydrate metabolism by decreasing insulin sensitivity and patients with acromegaly therefore have significant insulin resistance; thus, glucose tolerance may increase in some patients treated with SOMAVERT. No case of clinically relevant hypoglycaemia was observed in acromegalic patients with diabetes mellitus who were treated with SOMAVERT during the clinical studies; however, these patients should be carefully monitored and doses of anti-diabetic drugs reduced as necessary. (See DOSAGE AND ADMINISTRATION)

Growth Hormone Deficiency

SOMAVERT is a potent antagonist of growth hormone action. A state of functional growth hormone (GH) deficiency may result from administration of SOMAVERT, despite the presence of elevated serum GH levels, if serum IGF-I levels drop below the age-adjusted normal range. Serum IGF-I levels should therefore be monitored and maintained within the age-adjusted normal range by adjustment of the dose of SOMAVERT.

Pegvisomant has significant structural similarity to growth hormone (GH) which causes it to cross-react in commercially available GH assays. In addition, treatment with pegvisomant results in elevated growth hormone levels. SOMAVERT treatment should therefore not be monitored or adjusted based on serum GH concentrations. Instead, monitoring and dose adjustments should be based on serum IGF-I levels.

Liver Function Tests

Elevations of serum concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 10 times the upper limit of normal (ULN) were reported in two patients (0.8%) treated with SOMAVERT during the clinical studies. The event resolved in one patient upon dechallenge and recurred on rechallenge. A liver biopsy performed on the second patient was consistent with chronic hepatitis of unknown aetiology, which was considered unlikely to be related to SOMAVERT treatment. In both patients, the transaminase elevations normalised after discontinuation of SOMAVERT.

During the clinical studies, the incidence of elevations in ALT greater than 3 times but less than or equal to 10 times the ULN in patients treated with SOMAVERT and placebo were 1.2% and 2.1%, respectively.

The transaminase elevations did not appear to be related to the dose or duration of SOMAVERT treatment, generally occurred within 4 to 12 weeks of initiation of therapy, and were not associated with any identifiable biochemical, phenotypic, or genetic predictors.

Serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be monitored prior to the start of therapy with SOMAVERT, every 4 to 6 weeks for the first 6 months of therapy, and periodically thereafter, or at any time patients exhibit symptoms suggestive of hepatitis. Evidence of obstructive biliary tract disease should be ruled out in patients with elevation of ALT and AST, or in patients with a prior history of treatment with a somatostatin analogue. Treatment with SOMAVERT should not be initiated or continued if signs of liver disease are present, pending a comprehensive hepatic evaluation.

Carcinogenicity

A two year carcinogenicity study was performed in rats at subcutaneous doses up to 20 mg/kg/day. Malignant fibrous histiocytomas were found at injection sites in male rats only, but not in female rats, at doses ≥ 8mg/kg/day (producing 10-25 times the systemic exposure in humans at a dose of 0.3mg/kg/day). The incidence of these tumours was dose dependent and correlated with a dose dependent increase in irritation and inflammation at the injection sites. This response is consistent with literature reports of inert, nongenotoxic biomaterials producing this type of neoplasm in rodents after chronic subcutaneous injection, and the finding is not considered to indicate a carcinogenic hazard to humans.

Genotoxicity

SOMAVERT was not mutagenic in the Ames assays or clastogenic in the *in vitro* chromosomal aberration test in human lymphocytes.

Effects on Fertility

The effects of SOMAVERT on fertility and reproductive performance are not known. No study has been conducted in animals to investigate the effects of pegvisomant on fertility or general reproductive performance and there is no clinical experience of the use of SOMAVERT in women of reproductive age.

The therapeutic benefits of a reduction in IGF-I concentration, which results in improvements of the patient's clinical condition, could potentially increase fertility in female patients. Patients should be advised to use adequate contraception if necessary. SOMAVERT is not recommended during pregnancy (see Use in Pregnancy).

Use in Pregnancy

Pregnancy Category: B3

In studies in pregnant rabbits, pegvisomant was not teratogenic when administered subcutaneously during organogenesis at doses up to 10 mg/kg/day (5.5 times the maximum human therapeutic dose of 30 mg/day, based on body surface area). At 10 mg/kg/day, a reproducible small increase in post-implantation loss was observed. The potential developmental toxicity of pegvisomant has not been investigated in a second animal species. There are no studies in pregnant women. SOMAVERT should not be used in pregnancy unless the anticipated therapeutic benefit clearly outweighs the potential risk.

Use in Lactation

The potential effects of pegvisomant on postnatal development have not been investigated in animals. It is not known whether SOMAVERT is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when SOMAVERT is administered to a breastfeeding woman.

Use in Children

The safety and effectiveness of SOMAVERT in paediatric patients has not been established.

Use in the Elderly

Clinical studies of SOMAVERT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Use in Patients with Impaired Hepatic or Renal Function

The safety and effectiveness of SOMAVERT in patients with renal or hepatic insufficiency have not been established.

Effects on Laboratory Tests

Liver Function Tests:

Recommendations for monitoring liver function tests are stated above. (See PRECAUTIONS, Liver Function Tests)

IGF-I Levels:

Treatment with SOMAVERT should be evaluated by monitoring serum IGF-I concentrations four to six weeks after therapy is initiated or any dose adjustments are made and at least every six months after IGF-I levels have normalised. The goals of treatment should be to maintain a patient's serum IGF-I concentration within the age-adjusted normal range and to control the signs and symptoms of acromegaly.

GH Levels:

Pegvisomant has significant structural similarity to growth hormone (GH) which causes it to cross-react in commercially available GH assays. In addition, treatment with pegvisomant results in elevated growth hormone levels. SOMAVERT treatment should therefore not be monitored or adjusted based on serum GH concentrations. Instead, monitoring and dose adjustments should be based on serum IGF-I levels.

INTERACTIONS WITH OTHER MEDICINES

Interactions between SOMAVERT and other medicinal products have not been evaluated in formal studies.

Patients receiving insulin or oral hypoglycaemic medicinal products may require dose reduction of these therapeutic agents due to the effect of SOMAVERT on insulin sensitivity (see PRECAUTIONS, Glucose Metabolism and DOSAGE AND ADMINISTRATION)

In clinical studies, patients on opioids often needed higher serum pegvisomant concentrations to achieve appropriate IGF-I suppression compared with patients not receiving opioids. The mechanism of this interaction is not known.

Effects on Ability to Drive and Use Machines

No studies on the effect of SOMAVERT on the ability to drive and use machines have been performed.

ADVERSE EFFECTS

In clinical studies, the majority of adverse reactions to SOMAVERT were of mild to moderate intensity, of limited duration and did not require discontinuation of treatment. Most adverse events did not appear to be dose dependent.

Nine acromegalic patients (9.6%) withdrew from pre-marketing clinical studies because of adverse events, including two patients with marked transaminase elevations, one patient with lipohypertrophy at the injection sites, and one patient with substantial weight gain.

Table 2 shows the incidence of treatment-emergent adverse events that were reported in at least two patients treated with SOMAVERT and at frequencies greater than placebo during the 12-week, placebo-controlled study.

Table 2. Number of Patients (%) with Acromegaly Reporting Adverse Events in a 12-week Placebo-controlled Study with SOMAVERT[a]

Event	SOMAVERT			Placebo n=32
	10 mg/day n=26	15 mg/day n=26	20 mg/day n=28	
General Disorders and Administration Site Conditions				
Pain	2 (8%)	1 (4%)	4 (14%)	2 (6%)
Injection site reaction	2 (8%)	1 (4%)	3 (11%)	0
Oedema peripheral	2 (8%)	0	1 (4%)	0
Chest pain	1 (4%)	2 (8%)	0	0
Gastrointestinal Disorders				
Diarrhoea	1 (4%)	0	4 (14%)	1 (3%)
Nausea	0	2 (8%)	4 (14%)	1 (3%)
Infections and Infestations				
Influenza	1 (4%)	3 (12%)	2 (7%)	0
Infection[b]	6 (23%)	0	0	2 (6%)
Sinusitis	2 (8%)	0	1 (4%)	1 (3%)
Injury, Poisoning and Procedural Complications				
Injury	2 (8%)	1 (4%)	0	1 (3%)
Investigations				
Liver function tests abnormal	3 (12%)	1 (4%)	1 (4%)	1 (3%)
Musculoskeletal and Connective Tissue Disorders				
Back pain	2 (8%)	0	1 (4%)	1 (3%)
Nervous System Disorders				
Dizziness	2 (8%)	1 (4%)	1 (4%)	2 (6%)
Paresthesia	0	0	2 (7%)	2 (6%)
Vascular Disorders				
Hypertension	0	2 (8%)	0	0

[a] Table includes only those events that were reported in at least 2 patients and at a higher incidence in patients treated with SOMAVERT than in patients treated with placebo.

[b] The 6 events coded as "infection" in the group treated with SOMAVERT 10 mg were reported as cold symptoms (3), upper respiratory infection (1), blister (1), and ear infection (1). The 2 events in the placebo group were reported as cold symptoms (1) and chest infection (1).

Immunogenicity

The development of isolated low-titre non-neutralising anti-growth hormone antibodies was observed in 16.9% of patients treated with SOMAVERT. The clinical significance of these antibodies is unknown.

Post-marketing Experience

Occurrence of injection site hypersensitivity and injection site hypertrophy (e.g. lipohypertrophy) has been observed.

The following adverse reactions have been identified during post-approval use of SOMAVERT. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Immune system disorders: systemic hypersensitivity reactions including anaphylactic/anaphylactoid reactions, laryngospasm, angioedema, generalised skin reactions (rash, erythema, pruritis, urticaria). Some patients required hospitalisation.

DOSAGE AND ADMINISTRATION

Treatment should be initiated under the supervision of a physician experienced in the treatment of acromegaly.

It should be considered whether to continue treatment with somatostatin analogues as the use in combination with SOMAVERT has not been studied.

For the different dosage regimens the following strengths are available: SOMAVERT 10 mg, SOMAVERT 15 mg and SOMAVERT 20 mg.

Serum IGF-I levels should be obtained prior to initiating therapy. A loading dose of 80 mg of SOMAVERT should be administered subcutaneously under medical supervision. Thereafter, the patient should begin daily subcutaneous injections of 10 mg of SOMAVERT. Serum IGF-I levels should be obtained every 4 to 6 weeks and appropriate dose adjustments made in increments of 5 mg/day in order to maintain the serum IGF-I level within the age-adjusted normal range and alleviate the signs and symptoms of acromegaly.

The maximum daily maintenance dose should not exceed 30 mg.

The site of injection should be rotated daily to help prevent lipohypertrophy.

Diabetic Patients

During treatment with SOMAVERT, patients on anti-diabetic therapy may need reduced doses of insulin or oral hypoglycaemic agents because SOMAVERT increases insulin sensitivity and glucose tolerance. (See also PRECAUTIONS, Glucose Metabolism).

Elderly

Clinical studies of SOMAVERT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. (See PRECAUTIONS, Use in the Elderly).

Heavier individuals tend to have a higher total body clearance of pegvisomant than lighter individuals, and may thus require greater doses of pegvisomant. (See Pharmacokinetics, Metabolism and Excretion)

In clinical studies, patients on opioids often needed higher serum pegvisomant concentrations to achieve appropriate IGF-I suppression compared with patients not receiving opioids. The mechanism of this interaction is not known. (See PRECAUTIONS, Drug Interactions).

Instructions for Use and Handling

SOMAVERT is supplied as a lyophilised powder. Reconstitute SOMAVERT by injecting the diluent provided in the pack (sterile Water for Injections) into the vial of SOMAVERT powder, aiming the stream of liquid against the wall of the vial. Hold the vial and diluent syringe in one hand and gently swirl the liquid to dissolve the powder. **DO NOT SHAKE THE VIAL,** as this may cause denaturation of pegvisomant. After reconstitution, each vial contains 10, 15 or 20mg of pegvisomant in 1mL of solution. The solution should be clear after reconstitution. If the solution is cloudy or contains particles, do not inject it.

Detailed instructions for the preparation and administration of SOMAVERT are contained in the leaflet provided in the pack.

To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary, hold at 2ºC - 8ºC for not more than 6 hours.

This product contains no antimicrobial agent. SOMAVERT is for single use in one patient only. Discard any residue.

OVERDOSAGE

There is limited experience of overdosage with SOMAVERT. A patient who self-administered 80 mg/day of SOMAVERT for seven days did not show clinically significant adverse events that were considered related to the overdose.

In cases of overdose, administration of SOMAVERT should be discontinued and not resumed until IGF-I levels return to within or above the normal range.

PRESENTATION AND STORAGE CONDITIONS

SOMAVERT is supplied as lyophilised powder in glass vials and Water for Injections (diluent) in glass syringes. SOMAVERT is available in packs of:

10 mg: 30’s; 15 mg: 30’s and 20 mg: 1’s and 30’s.

Prior to reconstitution, SOMAVERT should be stored at 2ºC to 8ºC (Refrigerate. Do not freeze). The container should be kept in the outer carton in order to protect from light.

The reconstituted solution should be administered as soon as possible (within 6 hours).

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114

POISON SCHEDULE OF THE DRUG

S4 – Prescription only medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

9 December 2005

DATE OF MOST RECENT AMENDMENT

31 May 2017

® Registered Trademark