NAME OF THE DRUG

Ancestim is a human stem cell factor (SCF), produced by recombinant DNA technology. STEMGEN® is the Amgen Inc. trademark for ancestim (recombinant methionyl human stem cell factor, r-metHuSCF).

DESCRIPTION

STEMGEN® is a 166 amino acid protein produced by *Escherichia coli* (*E coli*) bacteria into which a gene has been inserted for soluble human stem cell factor. STEMGEN® has a monomeric molecular weight of approximately 18,500 daltons and normally exists as a noncovalently associated dimer. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine retained after expression in *E coli*. Because STEMGEN® is produced in *E coli*, the product is nonglycosylated.

STEMGEN® is a sterile, white, preservative-free, lyophilised powder for reconstitution and administration as a subcutaneous (SC) injection. Each single-use vial of STEMGEN® contains 1.875 mg of ancestim at a specific activity of 0.84 to 1.8 x 10^6 U/mg (as measured by a cell mitogenesis assay). Vials of STEMGEN® are reconstituted with 1.2 mL of sterile Water for Injection to yield an ancestim concentration of 1500 µg/mL. Reconstituted STEMGEN® is a sterile aqueous solution containing 4.5% mannitol and 0.5% sucrose buffered at pH 6.0 with 5 mM glutamic acid and 10 mM histidine.

PHARMACOLOGY

Pharmacokinetics

General

The pharmacokinetics of STEMGEN® are dose linear in the range of 5 to 30 µg/kg in both healthy volunteers and cancer patients. All serum concentrations given below are corrected for endogenous SCF levels measured at baseline.

Subcutaneous absorption: Absorption of STEMGEN® following SC administration as a single agent to healthy volunteers and cancer patients is first order and is characterised by an absorption half-life of approximately 35 to 41 hours following a mean lag time of 2 hours. Peak concentrations generally occur 15 to 24 hours postdose (range 8 to 36 hours) with mean serum concentrations of 3.6, 4.9 and 13.7 ng/mL following doses of 5 (n = 2), 10 (n = 8) and 25 µg/kg (n = 12) to cancer patients, similar to serum levels in healthy subjects administered STEMGEN®. The bioavailability in humans has not been determined since ancestim has not been administered intravenously. In nonhuman primates, the bioavailability is greater than 60%.

Distribution: Studies in rats demonstrate that, after intravenous (IV) administration, ancestim distributes primarily to plasma and kidneys initially, with subsequent rapid loss from all tissues.

Metabolism: When radiolabelled ancestim was administered to rats, 90% of the radioactivity was excreted in the urine. Ancestim was not quantifiable in rat urine using Enzyme-Linked Immunosorbent Assay (ELISA), indicating degradation to lower molecular weight products prior to excretion.

Elimination: In healthy volunteers and in cancer patients, the half-life of elimination is 2 to 5 hours. However, absorption is the rate limiting process so the half-life is 35 to 41 hours. Apparent clearance (CL/F) is approximately 35 to 40 mL/hour/kg.

Multiple dosing: Upon multiple daily dosing in cancer patients (5, 10, 25 and 50 µg/kg/day), serum levels achieve steady state after 4 or 5 days with approximately a two-fold increase in peak concentration and area under the curve (to 24 hours) at steady state, compared to corresponding values after the first dose. There is a concomitant decrease in time to peak concentration (7 hours on day 14). When STEMGEN® is co-administered with NEUPOGEN® (filgrastim), trough serum levels of STEMGEN® increase in proportion to dose (5 to 30 µg/kg/day) until approximately day 4 of dosing. Thereafter, the pharmacokinetics of STEMGEN® are altered such that trough levels decrease due to clearance induction, despite continued administration of STEMGEN®.

Special Populations

Paediatric: No paediatric pharmacokinetic data are available for STEMGEN®.

Gender: There have been no controlled comparisons of STEMGEN® pharmacokinetic parameters in males and females, however, there were no apparent differences in these parameters between male and female lung cancer patients.

Race: There were no apparent differences in STEMGEN® pharmacokinetic parameters between Japanese, Caucasian and African-American subjects.

Renal insufficiency: Based on animal studies, the kidney is the major elimination route of ancestim, and impaired renal function would be expected to cause increased serum concentrations. The clinical consequences of increased serum levels are unknown.

Other

At doses of 15 and 20 µg/kg/day, a statistically significant increase ($p = 0.025$) in mean trough STEMGEN® serum levels (approximately 2 ng/mL) was observed during the period of apheresis.

Drug Interactions

Over the dose ranges studied (5 to 30 µg/kg/day), STEMGEN® does not affect the pharmacokinetics of NEUPOGEN® (10 to 12 µg/kg/day). NEUPOGEN® alters the pharmacokinetics of STEMGEN® as outlined above (see MULTIPLE DOSING). It is unknown whether STEMGEN® interacts with other drugs.

Preclinical Experience

Haemopoietic growth factors, including SCF, are glycoproteins which act on haemopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation, commitment and/or functional activation.

Endogenous SCF is a multilineage haemopoietic growth factor which is produced by bone marrow fibroblasts. In humans, the serum concentration of soluble SCF averages 3.3 ± 1.1 ng/mL. Receptors for SCF are found on a range of early to more mature haemopoietic progenitor cells, as well as mast cells, melanocytes and germ cells. In vitro, recombinant SCF as a single agent shows little colony-stimulating activity on haemopoietic progenitor cells. However, it synergistically increases the colony-forming or stimulatory activity of numerous haemopoietic growth factors, including granulocyte colony-stimulating

factor (G-CSF), granulocyte macrophage colony-stimulating factor, erythropoietin, megakaryocyte growth and development factor, and interleukin-2. In vivo, recombinant SCF administration at high doses has been shown to stimulate multiple haemopoietic lineages in mice, dogs and primates. At lower doses, it synergises with recombinant G-CSF to mobilise peripheral blood progenitor cells (PBPC) capable of rescuing mice, dogs and primates from otherwise lethal irradiation. As a single agent in vivo and in vitro, recombinant SCF is a growth and activation factor for mast cells and can also stimulate melanocyte development and pigment production. SCF is relatively species-specific and the recombinant human molecule is approximately 500- to 1000-fold less active on rodent cells in vitro than the corresponding recombinant rodent SCF.

Acute and repeat-dose IV studies of ancestim have been conducted in cynomolgus monkeys and baboons. In these studies, severe anaphylactoid reactions occurred when doses of ancestim ≥ 40 µg/kg (baboons) or 6 mg/kg (monkeys) were administered by rapid IV injection. No such reactions were observed in primates administered any dose of SC ancestim in toxicology studies. A subsequent study in baboons indicated that these systemic allergic reactions could be prevented by prophylactic administration of H_1 and H_2 antihistamines along with either a corticosteroid or an inhaled bronchodilator.

Clinical Experience

In phase 1/2 studies involving 367 patients with breast cancer, non-Hodgkin's lymphoma and ovarian cancer, STEMGEN® administration over a dose range of 5 to 25 µg/kg/day in combination with a fixed dose of NEUPOGEN® resulted in a dose-dependent increase in circulating PBPC, including $CD34^+$ cells, granulocyte macrophage colony-forming units (CFU-GM) and erythroid burst-forming units (BFU-E), compared to NEUPOGEN® alone. STEMGEN® as a single agent did not cause substantial PBPC mobilisation at the only dose tested (5 µg/kg/day). For patients receiving the cytokine combination, this increase in circulating PBPC resulted in apheresis yields that were approximately two- to three-fold greater than those of patients receiving NEUPOGEN® alone. With discontinuation of STEMGEN® plus NEUPOGEN® therapy, PBPC levels returned to baseline, in most cases within 4 to 7 days. In a 219 patient phase 1/2 breast cancer study which utilised 3 fixed aphereses, 8% of patients treated with 20 µg/kg/day STEMGEN® plus NEUPOGEN® 10 µg/kg/day and 17% of patients treated with NEUPOGEN® alone, failed to reach a minimal number of $CD34^+$ cells (1×10^6/kg).

In the phase 3 controlled clinical trial, 205 breast cancer patients were randomised to receive either 20 µg/kg/day STEMGEN® SC in combination with 10 µg/kg/day NEUPOGEN® (n = 101) or 10 µg/kg/day NEUPOGEN® alone (n = 104). On day 5 of cytokine administration, apheresis was initiated. Apheresis and cytokine administration were continued daily until the target of 5×10^6 $CD34^+$ cells/kg (actual body weight) had been collected, up to a maximum of 5 aphereses. This target was based on results from a preceding phase 1/2 study in a comparable patient population which indicated that infusion of 5×10^6 $CD34^+$ cells/kg was correlated with a high probability of rapid platelet recovery (by day 14) and a low probability of delayed platelet recovery (≥ 28 days).

Treatment with STEMGEN® plus NEUPOGEN® caused a sustained mobilisation of PBPC resulting in greater $CD34^+$ cell collections and a greater proportion of patients reaching the target yield of 5×10^6 $CD34^+$ cells/kg (63%) compared to treatment with NEUPOGEN® alone (47%). This improved $CD34^+$ cell mobilisation provided a clinically and statistically significant reduction ($p = 0.038$) in the number of aphereses required to collect the target

number of PBPC. Patients receiving STEMGEN® plus NEUPOGEN® reached the target number of PBPC in a median of 4 apheresis procedures, while patients receiving NEUPOGEN® alone required a median of greater than or equal to 6 aphereses (ie, less than 50% of NEUPOGEN® -treated patients reached the collection target in 5 aphereses).

As expected for patients apheresed to the same target cell yield, the treatment groups showed similar haemopoietic recovery following high-dose chemotherapy and infusion of the collected PBPC with NEUPOGEN® support (10 µg/kg/day). The proportion of patients who failed to reach a minimal number of $CD34^+$ cells (1×10^6/kg) to allow high-dose chemotherapy with PBPC support (mobilisation failures) or experienced a delayed rise in platelets to 20×10^9/L (≥ 28 days) (engraftment failures), was lower for patients receiving STEMGEN® plus NEUPOGEN®, compared to those receiving NEUPOGEN® alone (3.5% vs 7.4%).

Several additional randomised, controlled studies also support the efficacy of STEMGEN®. A meta-analysis across all PBPC studies, including cytokine alone and chemotherapy plus cytokine mobilisation, showed that there was a highly signficant improvement ($p < 0.0001$) in each of the efficacy parameters, ie, 1) apheresis yields of $CD34^+$ cells, 2) numbers of patients with apheresis harvests ≥ 5×10^6 $CD34^+$ cells/kg and 3) number of aphereses required to collect 5×10^6 $CD34^+$ cells/kg for patients receiving STEMGEN® plus NEUPOGEN® compared to patients receiving NEUPOGEN® alone.

INDICATIONS

STEMGEN® is indicated for use in combination with NEUPOGEN® (filgrastim) in the setting of autologous peripheral blood progenitor cell (PBPC) transplantation for patients at risk of poor PBPC mobilisation to increase the number of PBPC collected in the apheresis harvest, thereby increasing the proportion of patients reaching a PBPC target for transplantation.

CONTRAINDICATIONS

Do not administer STEMGEN® by IV injection or infusion. STEMGEN® should only be administered by SC injection. STEMGEN® has not been administered IV to patients in any clinical setting. Preclinical animal studies demonstrated increased risk of systemic allergic reactions (greater incidence and severity) when STEMGEN® was administered by the IV route (see PRECLINICAL EXPERIENCE).

STEMGEN® is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, ancestim or any component of the product.

WARNINGS

STEMGEN® should only be administered in a setting with trained medical personnel who have appropriate medications and/or equipment necessary to treat life-threatening reactions if they occur. Patients should be observed for a minimum of 1 hour after administration of STEMGEN®.

During the period of STEMGEN® administration, all patients should be prophylactically medicated with H_1 and H_2 antihistamines and a bronchodilator to prevent or minimise the possibility of systemic allergic (ie, anaphylactoid) reactions (see DOSAGE AND ADMINISTRATION - PREMEDICATION).

Patients With a History of Severe Allergy or Asthma

Due to the possibility of mast cell stimulation, patients with the following conditions were not included in clinical trials of STEMGEN®:

- a history of anaphylaxis
- asthma
- recurrent urticaria
- recurrent angioedema
- mast cell diseases (such as systemic mastocytosis, urticaria pigmentosa or diffuse cutaneous mastocytosis)

It is not known whether these patients may be at increased risk of systemic allergic reactions related to STEMGEN® administration.

PRECAUTIONS

General

STEMGEN® is not recommended for monotherapy. Only the combination with NEUPOGEN® has been extensively studied in terms of safety and efficacy.

STEMGEN® is indicated for use only in patients who are at risk of inadequate PBPC mobilisation with NEUPOGEN® alone. Factors associated with such risk of inadequate mobilisation include the following:

- previous failure to mobilise adequately
- several previous cycles of chemotherapy
- previous chemotherapy with agents that are specifically toxic to stem cells
- extensive prior radiotherapy
- advanced stage of disease

Laboratory Monitoring

White blood cell (WBC) counts should be monitored after 4 days of STEMGEN® plus NEUPOGEN®, and NEUPOGEN® dose-modification should be considered for those patients who develop a WBC count > 100 x 10^9/L (see PRECAUTIONS - LEUKOCYTOSIS).

Use With Caution in the Following Circumstances

Simultaneous Use With Chemotherapy and Radiotherapy

The safety and efficacy of the combination of STEMGEN® and NEUPOGEN® given simultaneously with cytotoxic chemoradiotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemoradiotherapy, it is not recommended to use STEMGEN® in the period 24 hours before, to 24 hours after the administration of cytotoxic chemoradiotherapy (see DOSAGE AND ADMINISTRATION).

Growth Factor Potential

STEMGEN® is a growth factor that stimulates haemopoietic progenitor cells, mast cells and melanocytes. Stimulation of small cell lung carcinoma cell lines and acute myelogenous leukaemia cells has also been observed in vitro in some studies. Although STEMGEN® is intended to be administered prior to high-dose chemoradiotherapy, the possibility that STEMGEN® can act as a growth factor for any tumour type, particularly myeloid malignancies, melanomas, small cell lung cancers and basophilic or mast cell leukaemias cannot be excluded. Therefore, precaution should be exercised in using STEMGEN® in these diseases.

Paediatric Use

The safety and efficacy of STEMGEN® in paediatric cancer patients have not been established. At least 7 patients under age 12 have been treated with STEMGEN®, with or without NEUPOGEN®, in clinical trials of patients with bone marrow failure syndromes. In these small number of patients, there has been no apparent increase in the incidence or severity of adverse events in premedicated paediatric patients.

Tumour Contamination of Apheresis Product

Malignant cells from a variety of solid tumours are known to enter the circulation on some occasions, and may be collected by apheresis in patients undergoing mobilisation with haemopoietic growth factors. The effect of re-infusion of tumour cells has not been well-studied, and the limited data available are inconclusive. The phase 3 trial described above (see CLINICAL EXPERIENCE) found no difference in the incidence of breast cancer contamination in apheresis products from patients mobilised with STEMGEN® in combination with NEUPOGEN®, compared to those from patients mobilised with NEUPOGEN® alone.

Leukocytosis

White blood cell counts of $\geq 100 \times 10^9$/L were observed in approximately 13% of patients receiving STEMGEN® plus NEUPOGEN® for PBPC mobilisation, compared with 1% of patients receiving NEUPOGEN® alone. Most of these occurrences were when cytokine administration exceeded 7 days. There were no reports of adverse events associated with this degree of leukocytosis and counts decreased rapidly with cessation of NEUPOGEN®. However, in view of the potential risks associated with severe leukocytosis, the WBC count should be monitored frequently. It is recommended that cytokine administration be discontinued if the leukocyte count rises to $> 100 \times 10^9$/L (see PRECAUTIONS - LABORATORY MONITORING).

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of STEMGEN® has not been studied.

STEMGEN® was not genotoxic in assays for gene mutations (*Salmonella typhimurium* and *E coli*) or chromosomal damage (mouse bone marrow cytogenetics and mouse micronucleus assay).

Reproductive studies in male and female monkeys showed no evidence of impaired fertility at doses up to 500 µg/kg and 1000 µg/kg SC, respectively (approximately 5 and 8 times human exposure at the maximum recommended clinical dose of 20 µg/kg based on AUC, respectively).

Use in Pregnancy

Pregnancy Category: B2

Reproductive studies in pregnant and nursing monkeys have revealed no evidence of foeto-toxic or teratogenic effects on foetuses when STEMGEN® was administered by daily SC injection during the period of organogenesis at dose levels up to 1 mg/kg/day, or during the prenatal and postnatal periods at dose levels up to 300 µg/kg/day (approximately 5 and 2 times human exposure at the maximum recommended clinical dose of 20 µg/kg based on AUC, respectively). Reproductive studies using ancestim and NEUPOGEN® have not been conducted by the company.

Because animal reproduction studies are not always predictive of human response, STEMGEN® should be used during pregnancy only if clearly needed.

Use in Lactation

It is not known whether STEMGEN® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if STEMGEN® is administered to a nursing woman.

Interactions With Other Drugs

Drug interactions between STEMGEN® and other drugs (including cytokines other than NEUPOGEN®) have not been fully evaluated. The potential for interaction with drugs, such as radiocontrast agents, which may potentiate the release of histamine or other mast cell mediators, is unknown.

Effects on Laboratory Tests

In clinical trials, the following laboratory results were observed.

- In patients receiving STEMGEN® with NEUPOGEN®, the WBC count was similar to that in patients receiving NEUPOGEN® alone over the same time periods. In addition, numbers of red blood cells, platelets, eosinophils and basophils in patients receiving STEMGEN® plus NEUPOGEN® were comparable to those in patients receiving NEUPOGEN® alone.

- Platelet counts were generally within normal limits prior to STEMGEN® plus NEUPOGEN® therapy. With STEMGEN® plus NEUPOGEN® therapy for PBPC mobilisation, platelet counts were generally stable prior to apheresis, but, as expected, decreased during the apheresis procedures in both control patients and patients receiving STEMGEN® plus NEUPOGEN®.

- In some trials of STEMGEN® in combination with NEUPOGEN®, there were increases in serum uric acid, lactate dehydrogenase and serum alkaline phosphatase beyond those observed with NEUPOGEN® alone. No clinical events related to these increases have been reported.

ADVERSE REACTIONS

STEMGEN® is generally well-tolerated. In clinical trials, over 400 patients received STEMGEN® (5 to 30 µg/kg/day) in combination with NEUPOGEN® (5 to 12 µg/kg/day) for PBPC mobilisation. In this setting, STEMGEN® was administered with a premedication

regimen consisting of H_1 and H_2 antihistamines and an inhaled bronchodilator, with or without pseudoephedrine.

Experience in the Phase 3 Trial

In the phase 3 randomised, controlled trial of STEMGEN® in combination with NEUPOGEN® in patients with breast cancer, a total of 204 patients received cytokine (100 patients received STEMGEN® at 20 µg/kg/day with NEUPOGEN® at 10 µg/kg/day and 104 patients received NEUPOGEN® alone at 10 µg/kg/day). The following adverse events were reported during the mobilisation phase of the study with greater than a 5% difference between treatment groups.

Frequency of Adverse Events in the Phase 3 Study

% of Patients with Events		
Body System **Event**	**STEMGEN® plus NEUPOGEN®** **n = 100**	**NEUPOGEN® Alone** **n = 104**
Application Site		
Injection site reactions	Very common (92%)	Very common (10%)
Central & Peripheral Nervous System		
Paresthesia	Very common (29%)	Very common (35%)
Headache	Very common (13%)	Very common (23%)
Dizziness	Very common (12%)	Common (6%)
Gastrointestinal		
Nausea	Very common (16%)	Very common (23%)
Heart Rate/Rhythm		
Tachycardia	Common (8%)	0%
Respiratory		
Respiratory symptoms	Very common (28%)	Very common (16%)
Skin & Appendages		
Distant skin reactions	Very common (21%)	Common (7%)

Systemic Allergic Reactions

There were no life-threatening or fatal adverse events attributed to STEMGEN® therapy. There were 3 systemic allergic reactions in patients who received STEMGEN® plus NEUPOGEN® for PBPC mobilisation. These reactions developed within 4 to 12 hours after injection; none occurred on the first dose of STEMGEN®. One patient, who was noncompliant with the H_1 and H_2 antihistamine regimen, developed cough, dyspnea, hoarseness and throat tightness. A second patient developed generalised urticaria and the third patient experienced a multisymptom reaction which included angioedema, throat tightness, dyspnea, nausea/vomiting and fever. Symptoms resolved after treatment with steroids and/or additional antihistamines. Transient mild tachycardia (heart rate 90 to 145 bpm), which did not require clinical treatment, was reported in 8 of 100 patients following administration of STEMGEN® plus NEUPOGEN®, with premedications.

Experience Across All Studies

The most common adverse event reported in patients receiving STEMGEN® in combination with NEUPOGEN® (n = 434) was mild-to-moderate injection site reactions, reported in 84% of patients. Acute injection site symptoms were predominantly events of erythema (59%), pruritus (25%) and urticaria (16%). Hyperpigmentation and rash at the injection site have also been observed. These reactions are generally small in diameter; however, in rare cases, reactions as large as 10 x 10 cm have been reported. Onset of the local reaction has been described to occur within 60 minutes and up to 24 hours after the injection and resolve within 24 to 48 hours. A recall phenomenon has also been described in a few patients in which erythema occurs or recurs at a previous distant injection site following a subsequent injection. Local reactions generally did not require treatment, however, a few patients were treated with topical steroid creams and rarely, additional H_1 antihistamines. Other mild-to-moderate skin reactions (distant from the injection site) including pruritus, rash and urticaria, were reported in 18% of patients receiving STEMGEN® plus NEUPOGEN® compared to 5% of patients receiving NEUPOGEN® alone. Musculoskeletal symptoms, primarily skeletal pain, were reported in 48% of patients, similar to the incidence with NEUPOGEN® alone.

Mild-to-moderate respiratory symptoms, such as pharyngitis, dyspnea and cough, were reported in 25% of patients receiving STEMGEN® plus NEUPOGEN®, compared to 14% of patients receiving NEUPOGEN® alone.

Overall, of 687 patients treated with STEMGEN® at < 30 µg/kg/day (including 349 at 20 µg/kg/day) in clinical trials, 5% experienced systemic allergic reactions. Ten of 37 (27%) patients treated with STEMGEN® at 30 to 100 µg/kg/day experienced systemic allergic reactions.

With premedication, these reactions, occurring on initial or subsequent SC injections, have been reported in 16 of 516 patients (approximately 4% in patients receiving 20 µg/kg/day) treated with STEMGEN® in clinical trials for PBPC mobilisation. These reactions have been limited to skin symptoms only (generalised urticaria) in 3 of these 16 patients. The remaining events have generally been characterised by symptoms involving at least 2 body systems, most often skin (urticaria, pruritus) and respiratory (dyspnea, cough, hoarseness, throat tightness). Angioedema and cardiovascular symptoms (tachycardia, hypotension, chest pain) have also been observed. In 2 patients, these reactions occurred on initial exposure.

Systemic allergic reactions are generally moderate to severe with life-threatening reactions reported rarely. Reactions were usually delayed relative to the SC administration; most occurred within 12 hours after administration. Resolution of symptoms occurred after administration of additional antihistamines and/or corticosteroids. Infrequently, bronchodilators and adrenaline have been used to treat these reactions. A few reactions have occurred with rapid onset requiring immediate medical intervention.

Symptoms may recur in patients who are rechallenged, although not always on the next dose. **In cases of severe reactions, rechallenge is not recommended.**

In these trials, there were no reports of pleuritis, pericarditis or capillary leak syndrome related to STEMGEN®, as seen with certain other cytokines.

Nine percent of patients tested (23 of 258) showed seroreactivity to STEMGEN®. No patients in any study exhibited any clinical sequelae or other unusual adverse events that would be expected for an antibody reaction or serum sickness.

DOSAGE AND ADMINISTRATION

STEMGEN® and NEUPOGEN® should not be administered in the period 24 hours before to 24 hours after the administration of chemotherapy (see PRECAUTIONS). STEMGEN® should not be administered without NEUPOGEN®. However, STEMGEN® and NEUPOGEN® must be administered as separate injections, at different sites.

STEMGEN® should only be administered in a setting with trained medical personnel who have appropriate medications and/or equipment necessary to treat life-threatening reactions if they occur. Patients should be observed for a minimum of 1 hour after administration of STEMGEN®.

The recommended dose of STEMGEN®, for use with NEUPOGEN®, for the mobilisation of PBPC is:

Cytokine Only Mobilisation

STEMGEN® 20 µg/kg/day as an SC bolus injection and NEUPOGEN® 10 µg/kg/day SC. STEMGEN® and NEUPOGEN® should be administered until completion of apheresis. In cytokine-alone mobilisation regimens, daily administration of STEMGEN® plus NEUPOGEN® with daily aphereses beginning on day 5 was found to be safe and effective (see CLINICAL EXPERIENCE). It is recommended that this daily dose of STEMGEN® is not exceeded (see ADVERSE REACTIONS).

Post Chemotherapy Mobilisation

STEMGEN® 20 µg/kg/day as an SC bolus injection and NEUPOGEN® 5 µg/kg/day SC, starting 24 hours after completion of chemotherapy and continuing until the completion of apheresis. Beginning aphereses on the day the WBC count rises to $\geq 4 \times 10^9$/L has been shown to be safe and effective in clinical trials (see CLINICAL EXPERIENCE). It is recommended that this daily dose of STEMGEN® is not exceeded (see ADVERSE REACTIONS).

Premedication

Patients receiving STEMGEN® must be premedicated with H_1 and H_2 antihistamines and a bronchodilator (beta agonist). In clinical trials, either diphenhydramine (50 mg orally every 6 hours) or cetirizine (10 mg orally once daily) was used most frequently as the H_1 antihistamine, ranitidine (150 mg orally every 12 hours or 300 mg orally once daily) was the most commonly used H_2 antihistamine, and salbutamol inhaler (2 puffs, 30 to 60 minutes prior to each injection) was used as the bronchodilator. Administration of H_1 and H_2 antihistamines should start 12 to 24 hours prior to the first injection of STEMGEN®. Further administration should be timed such that a dose is given 60 to 90 minutes prior to each STEMGEN® injection, and should continue until 48 hours after the last injection.

Reconstitution and Dilution

STEMGEN® is a sterile, white, preservative-free, lyophilised powder suitable for SC bolus injection upon reconstitution. **STEMGEN® should not be administered IV (see CONTRAINDICATIONS)**. No information is available on continuous SC infusion of

reconstituted STEMGEN®. STEMGEN® must be reconstituted with 1.2 mL sterile Water for Injection. When reconstituted with 1.2 mL sterile Water for Injection, the final concentration of STEMGEN® is 1500 µg/mL. During reconstitution, the vial contents may be gently swirled to avoid foaming during dissolution. Avoid excess or vigorous agitation; do not shake.

STEMGEN® must be used within 24 hours of reconstitution. Use only one dose per reconstituted vial; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration; if particulates or discolouration are observed, the contents of the container should not be used.

OVERDOSAGE

The maximum tolerated dose of STEMGEN®, when administered with premedications, has not been determined. However, 10 of 37 patients (27%) treated with STEMGEN® at 30 to 100 µg/kg/day experienced systemic allergic reactions. This suggests that the incidence of systemic allergic reactions may be dose-related (see ADVERSE REACTIONS). The recommended dose of STEMGEN®, for use with NEUPOGEN®, for PBPC mobilisation is 20 µg/kg/day.

STORAGE

Powder for Injection: STEMGEN® sterile powder should be stored in the refrigerator at 2°C to 8°C (Refrigerate. Do not freeze). Lyophilised STEMGEN® powder is stable for 3 days at 29°C, with no observable decrease in activity or change in protein integrity.

Reconstituted Solution: When reconstituted with 1.2 mL sterile Water for Injection under aseptic conditions, STEMGEN® is stable for 24 hours at 29ºC, with no observable decrease in activity or change in protein integrity. However, for microbiological reasons the reconstituted solution should be used as soon as practicable after reconstitution/preparation. If storage of the reconstituted solution is necessary, hold at 2ºC to 8ºC (Refrigerate. Do not freeze) for not more than 24 hours. Prior to injection, STEMGEN® may be allowed to reach room temperature.

PRESENTATION

STEMGEN® 1.875 mg: Dispensing packs of 3 single-dose, preservative-free vials containing 1.875 mg of ancestim.

Name and Address of Manufacturer:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
USA

Name and Address of Sponsor:

Amgen Australia Pty Ltd
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NORTH RYDE NSW 2113
ABN 31 051 057 428

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