PRODUCT MONOGRAPH

STEMGEN®

(ancestim)

Sterile, Lyophilized Powder for Reconstitution

Subcutaneous Use Only

(1875 mcg/vial)

Hematopoietic Agent

BioVitrum AB
SE-11276
Stockholm, Sweden

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THERAPEUTIC CLASSIFICATION

Hematopoietic Agent

Caution: STEMGEN® may cause severe or life-threatening systemic allergic reactions (see WARNINGS).

ACTION AND CLINICAL PHARMACOLOGY

General

STEMGEN® (ancestim) is recombinant-methionyl human stem cell factor (r-metHuSCF), a homologue of endogenous human stem cell factor (SCF), produced by recombinant DNA technology.[1] Hematopoietic growth factors, including SCF, are glycoproteins, which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation, commitment, and/or functional activation. Receptors for SCF are found on a range of early to more mature hematopoietic progenitor cells, as well as mast cells, melanocytes, and germ cells.

Endogenous SCF is a multilineage hematopoietic growth factor which is produced by bone marrow fibroblasts.[2,3] In humans, the serum concentration of soluble SCF averages 3.3 ± 1.1 ng/mL.[2,3]

Pharmacologic Effects of STEMGEN® (ancestim) in Combination With NEUPOGEN® (filgrastim)

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 mcg/kg/day in combination with a fixed dose of NEUPOGEN® resulted in a dose-dependent increase in circulating peripheral blood progenitor cells (PBPC) compared to NEUPOGEN® alone.[4] The PBPCs included $CD34^+$ cells, granulocyte macrophage colony-forming units (CFU-GM), and erythroid burst-forming units (BFU-E). 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. STEMGEN® as a single agent did not cause substantial PBPC mobilization at theonly dose tested (5 mcg/kg/day).[4]

In patients receiving STEMGEN® with NEUPOGEN® and in patients receiving NEUPOGEN® alone over the same time period, there was a similar increase in white blood cell (WBC) count. WBC levels returned to baseline with discontinuation of STEMGEN® and NEUPOGEN®. In all studies to date, numbers of red blood cells (RBC), platelets, eosinophils, and basophils in patients receiving STEMGEN® plus NEUPOGEN® were comparable to those in patients receiving NEUPOGEN® alone.

Pharmacokinetics

General: The pharmacokinetics of STEMGEN® are dose-linear in the range of 5 to 30 mcg/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 subcutaneous (SC) administration as a single agent to healthy volunteers and cancer patients is first order and is characterized 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 mcg/kg (n = 12) to cancer patients, similar to serum levels in healthy volunteers administered STEMGEN®. The bioavailability in humans has not been determined since STEMGEN® has not been administered intravenously (IV). In nonhuman primates, the bioavailability is greater than 60%.

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

Metabolism: Studies in nephrectomized rats and studies of radiolabeled ancestim in normal rats demonstrated that ancestim is approximately 90% cleared by the kidney. Ancestim was not quantifiable in rat urine using ELISA, indicating degradation to lower molecular weight products.

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 terminal half-life is 35 to 41 hours. Relative clearance is approximately 35 to 40 mL/hour/kg.

Multiple dosing: Upon multiple daily dosing of STEMGEN® in cancer patients (5, 10, 25, and 50 mcg/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 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®, trough serum levels of STEMGEN® increase in proportion to dose (5 to 30 mcg/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

Pediatric: No pediatric 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.

Drug Interactions

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

Other

At doses of 15 and 20 mcg/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.

INDICATIONS AND CLINICAL USE

STEMGEN® (ancestim) is indicated for use in combination with NEUPOGEN® (filgrastim) to provide a sustained increase in the number of PBPC capable of engraftment, to increase the proportion of patients reaching a PBPC target, and to reduce the number of aphereses required to collect a target number of PBPC. STEMGEN® is to be used for mobilization of progenitor cells from the bone marrow to the peripheral blood in combination with NEUPOGEN®, with or without PBPC-mobilizing chemotherapy. The harvested progenitor cells can be used for transplant following myelosuppressive or myeloablative therapies.

Infusion of higher numbers of PBPC is associated with a higher probability of rapid engraftment following high-dose chemo-radiotherapy (see PHARMACOLOGY).

CONTRAINDICATIONS

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

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

WARNINGS

STEMGEN® (ancestim) should only be administered in a setting with trained medical personnel who have the appropriate medications and/or equipment necessary to treat life-threatening systemic allergic 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 minimize the possibility of systemic allergic (ie, anaphylactoid) reactions. Patients must be informed of the importance of taking the prescribed antihistamine and bronchodilator premedications in the period 24 hours before the first through 48 hours after the last administration of STEMGEN®. (see DOSAGE AND ADMINISTRATION - PREMEDICATION and PRECAUTIONS - Information for Patients). Patients should be instructed to immediately inform the staff if they develop symptoms of a systemic allergic reaction.

The recommended dosage must not be exceeded.

Overall, of 687 patients treated with STEMGEN® at < 30 mcg/kg/day (including 349 at 20 mcg/kg/day) in clinical trials, 5% experienced systemic allergic reactions. Ten of 37 patients treated with STEMGEN® at 30 to 100 mcg/kg/day experienced systemic allergic events. The incidence in PBPC studies in which patients received a standard premedication regimen, and in which patients were excluded if they had a history of severe allergic disorders was 16 of 516 or approximately 3% (4% in patients receiving 20 mcg/kg/day STEMGEN®). These reactions have been limited to skin symptoms only (generalized urticaria) in 3 of these 16 patients. The remaining events have generally been characterized by symptoms involving at least two body systems, most often skin (urticaria, pruritus) and respiratory (dyspnea, hoarseness, throat tightness). Angioedema and cardiovascular symptoms (tachycardia, hypotension) have also been observed. In two patients, these reactions occurred on initial exposure. Reactions usually were somewhat delayed relative to the SC administration; most occurred within 2 hours after administration. Resolution of symptoms occurred after administration of additional antihistamines and/or corticosteroids. Infrequently, bronchodilators and epinephrine have been used in treating these reactions. 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 other clinical trials, there have been a few cases of severe or life-threatening systemic allergic reactions in patients treated with STEMGEN® in which the reactions have been rapid in onset.

For the reasons stated above, patients with a history of anaphylaxis, asthma, recurrent urticaria, recurrent angioedema, or mast cell diseases (such as systemic mastocytosis, urticaria pigmentosa, or diffuse cutaneous mastocytosis) were not included in clinical trials of STEMGEN®. It is not known whether these patients may be at increased risk of systemic allergic reactions related to STEMGEN® administration.

PRECAUTIONS

General

STEMGEN® should be used by physicians experienced with progenitor cell mobilization techniques. STEMGEN® should only be administered in a setting with trained medical personnel who have the appropriate medications and/or equipment necessary to treat life-threatening systemic allergic reactions if they occur. Patients should be observed in the hospital for a minimum of 1 hour after administration of STEMGEN®.

Simultaneous Use With Chemo-radiotherapy

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

Leukocytosis

WBC counts of ≥ 100 x 10^9/L were observed in approximately 13% of patients receiving STEMGEN® plus NEUPOGEN® for PBPC mobilization, compared with 1% of patients receiving NEUPOGEN® alone. Most of these occurred 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® administration.

Laboratory Monitoring

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

Drug Interactions

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.

Growth Factor Potential

STEMGEN® is a growth factor that stimulates hematopoietic progenitor cells, mast cells,and melanocytes. Stimulation of small cell lung carcinoma cell lines and acute myelogenous leukemia cells has also been observed in vitro in some studies. Although STEMGEN® is intended to be administered prior to high-dose chemo-radiotherapy, the possibility that STEMGEN® can act as a growth factor for any tumor type, particularly myeloid malignancies, melanomas, small cell lung

cancers, and basophilic or mast cell leukemias cannot be excluded. Therefore, precaution should be exercised in using STEMGEN® in these diseases.

When STEMGEN® is used with NEUPOGEN® to mobilize PBPC, tumor cells may be collected in the apheresis product. The effect of re-infusion of tumor cells has not been well-studied, and the limited data available are inconclusive. The phase 3 trial (see PHARMACOLOGY) found no difference in the incidence of breast cancer contamination in apheresis products from patients mobilized with STEMGEN® in combination with NEUPOGEN® (3% of patients), compared to those from patients mobilized with NEUPOGEN® alone (5% of patients).

Carcinogenesis, Mutagenesis

The carcinogenic potential of STEMGEN® has not been studied. STEMGEN® failed to induce bacterial gene mutations in either the presence or absence of a drug metabolizing enzyme system. Similarly, STEMGEN® did not increase the incidence of chromosomal abnormalities or micronuclei in bone marrow or peripheral blood erythrocytes in mice.

Impairment of Fertility

STEMGEN® had no observed effect on the fertility of male monkeys at doses up to 500 mcg/kg nor on the fertility of female monkeys, nor on gestation, at doses up to 1000 mcg/kg.

Use in Pregnancy

Reproduction studies have been performed in monkeys at doses up to 50 times the recommended human dose and have revealed no evidence of impaired fertility or harm to the fetus due to STEMGEN®. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response, therefore caution should be exercised if STEMGEN® is administered during pregnancy (see TOXICOLOGY).

Nursing Mothers

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

Use in Children

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

Geriatric Use

Clinical studies of STEMGEN® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. At least nine geriatric cancer patients have been treated with STEMGEN® in clinical trials. There has been no apparent increase in the incidence or severity of adverse events in premedicated geriatric patients.

Information for Patients

Patients must be informed of the importance of taking the prescribed antihistamine and bronchodilator premedications in the period 24 hours before the first, through 48 hours after the last administration of STEMGEN®. Patients should be instructed to immediately inform the staff if they develop symptoms of a systemic allergic reaction. If a reaction occurs when a patient has left the hospital they should be informed to contact their physician immediately. If the reaction is very severe and the patient is having difficulty breathing or swallowing, they should be instructed to contact emergency medical personnel immediately. Because of the possibility of allergic reactions patients should be instructed to keep their premedications with them at all times.

ADVERSE REACTIONS

STEMGEN® (ancestim) is generally well-tolerated. In clinical trials, over 500 patients received STEMGEN® (5 to 30 mcg/kg/day) in combination with NEUPOGEN® (filgrastim)(5 to 12 mcg/kg/day) for PBPC mobilization. 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. The most frequent adverse events reported in patients receiving STEMGEN® in combination with NEUPOGEN® were mild-to-moderate injection site reactions, reported in 81% of patients. Musculoskeletal symptoms, primarily skeletal pain, were reported in 48% of patients, similar to the incidence with NEUPOGEN® alone. Acute injection site symptoms were predominantly events of erythema (56%), pruritus (23%), and urticaria (15%). Hyperpigmentation at the injection site has also been observed. Other mild-to-moderate skin reactions (distant from the injection site) including pruritus, rash, and urticaria were reported in 19% of patients receiving STEMGEN® plus NEUPOGEN® versus 4% of patients receiving NEUPOGEN® alone. Mild-to-

moderate respiratory symptoms, such as pharyngitis, dyspnea, and cough, were reported in 27% of patients receiving STEMGEN® plus NEUPOGEN®, compared to 16% of patients receiving NEUPOGEN® alone.

In clinical trials of PBPC mobilization, approximately 3% of patients receiving STEMGEN® in combination with NEUPOGEN® experienced systemic allergic reactions (see WARNINGS). In these trials, there were no reports of pleuritis, pericarditis, or capillary leak syndrome related to STEMGEN® or NEUPOGEN®, as seen with certain other cytokines.

In the phase 3 randomized, controlled trial of STEMGEN® in combination with NEUPOGEN® in patients with breast cancer (n = 204 patients receiving cytokine), the following adverse events were reported during the mobilization phase of the study (20 mcg/kg/day STEMGEN® with 10 mcg/kg/day NEUPOGEN® versus 10 mcg/kg/day NEUPOGEN® alone) with greater than a 5% difference between treatment groups.

Frequency of Adverse Events in the Phase 3 Study

Event	**% of Patients with Events**	
	STEMGEN® Plus NEUPOGEN® (n = 100)	**NEUPOGEN® Alone (n = 104)**
Injection site reactions	92%	10%
Paresthesia	29%	35%
Respiratory symptoms	28%	16%
Distant skin reactions	21%	7%
Nausea	16%	23%
Headache	13%	23%
Dizziness	12%	6%
Tachycardia	8%	0%

In the phase 3 clinical trial, there were no life-threatening or fatal adverse reactions attributed to STEMGEN® therapy. There were three systemic allergic reactions in patients who received STEMGEN® plus NEUPOGEN® for PBPC mobilization. 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 generalized urticaria, and the third patient had a multisymptom reaction which included angioedema, throat tightness, dyspnea, nausea/vomiting, and fever. Symptoms resolved after treatment with steroids and/or additional antihistamines.

In other clinical trials, there have been a few cases of severe or life-threatening

systemic allergic reactions in patients treated with STEMGEN® in which the reactions have been rapid in onset.

Transient mild tachycardia (heart rate 90 to 145 bpm), which did not require clinical treatment, was reported in 8 of 100 patients in the phase 3 clinical study following administration of STEMGEN® plus NEUPOGEN®, with premedications.

Nine percent of patients tested (23 of 258) showed seroreactivity to ancestim. Generally, titers were low and there was no relationship to dose. 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The maximum tolerated dose of STEMGEN® (ancestim), when administered with premedications, has not been determined; however, the incidence of systemic allergic reactions appears to be dose-related.
Overall, of 687 patients treated with STEMGEN® at < 30 mcg/kg/day (including 349 at 20 mcg/kg/day) in clinical trials, 5% experienced systemic allergic reactions. Ten of 37 patients treated with STEMGEN® at 30 to 100 mcg/kg/day experienced systemic allergic reactions.

DOSAGE AND ADMINISTRATION

The recommended dose of STEMGEN® (ancestim), for use in combination with NEUPOGEN® (filgrastim) for the mobilization of PBPC, is 20 mcg/kg/day as a SC injection. For the correct use of NEUPOGEN®, please refer to the NEUPOGEN® product monograph. STEMGEN® should not be administered without NEUPOGEN®. However, STEMGEN® and NEUPOGEN® must be administered as separate injections, at different sites. STEMGEN® **should not be used at doses above the recommended dose.**

In cytokine-alone mobilization regimens, daily administration of STEMGEN® plus NEUPOGEN® with daily aphereses beginning on day 5 was found to be safe and effective (see PHARMACOLOGY for schedules used in clinical trials). 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.

In chemotherapy-based mobilization regimens, daily STEMGEN® plus NEUPOGEN® should be initiated 24 hours after the administration of cytotoxic chemotherapy. Beginning aphereses on the day the WBC count rises through 4 x 10^9/L has been shown to be effective in clinical trials (see PHARMACOLOGY).

STEMGEN® should not be administered IV (see CONTRAINDICATIONS). No information is available on continuous SC infusion of STEMGEN®. STEMGEN® should only be administered by SC injection and must be reconstituted with 1.2 mL sterile Water for Injection, USP (see PHARMACEUTICAL INFORMATION).

STEMGEN® should only be administered in a setting with trained medical personnel who have the appropriate medications and/or equipment necessary to treat life-threatening systemic allergic reactions if they occur. STEMGEN® should not be self-administered.

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.

PHARMACEUTICAL INFORMATION

Proper Name: STEMGEN®

Chemical Name: Recombinant-methionyl human stem cell factor (r-metHuSCF)

Common Name: ancestim (USAN)

STEMGEN® is a 166 amino acid protein produced by *E coli* bacteria into which a gene has been inserted for soluble human stem cell factor. STEMGEN® normally exists as a noncovalently associated dimer.[1] The theoretical molecular weight of the monomer is 18,657 daltons. 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*. STEMGEN® is produced in *E coli* and therefore is nonglycosylated. The molecular formula of the STEMGEN® monomer is $C_{831}H_{1325}N_{211}O_{256}S_9$, the formula for the nonreduced noncovalently-linked dimer is exactly double ($C_{1662}H_{2650}N_{422}O_{512}S_{18}$). The specific activity (as measured by a cell mitogenesis assay) is 0.84 to 1.8 x 10^6 U/mg.

Composition

STEMGEN® is a sterile, white, preservative-free, lyophilized powder for reconstitution and administration as a SC injection. Each single-use vial of STEMGEN® contains 1875 mcg of ancestim. Vials of STEMGEN® are reconstituted with 1.2 mL of sterile Water for Injection to yield an ancestim concentration of 1500 mcg/mL with a withdrawable volume of 1.0 mL. Reconstituted STEMGEN® is a sterile aqueous solution of 10 mM histidine, 5 mM glutamic acid buffer at pH 6.0, containing 4.5% mannitol and 0.5% sucrose.

Reconstitution and Dilution

STEMGEN® must be reconstituted with 1.2 mL sterile Water for Injection, USP (without preservative). Compatibility of with saline or other diluents is unknown. During reconstitution, the vial contents may be gently swirled to avoid foaming during dissolution. Avoid excess or vigorous agitation; do not shake.

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

Stability and Storage Recommendations

STEMGEN® as a sterile powder should be stored in the refrigerator at 2° to 8° C (36° to 46° F). Do not freeze. Any vial of STEMGEN® powder left at room temperature for more than 72 hours should be discarded. Do not use after the expiry date.

STEMGEN® should be used immediately after reconstitution; although not recommended, STEMGEN® may be used up to 24 hours after reconstitution when stored at 2° to 8°C (36° to 46°F). Avoid shaking. Prior to injection, reconstituted STEMGEN® may be allowed to reach room temperature.

Use only one dose per reconstituted vial; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

AVAILABILITY OF DOSAGE FORMS

STEMGEN® (ancestim) is supplied in vials as a sterile lyophilized powder formulation containing 1875 mcg ancestim. Each dispensing package contains three vials of STEMGEN®.

INFORMATION FOR THE PATIENT

Please alert your relative or friend who may be with you to the possible allergic reactions with STEMGEN® (ancestim).

What is STEMGEN® and how does it work?
As part of your medical treatment for your cancer, your doctor has advised you to undergo a peripheral blood progenitor cell (PBPC) transplant. When a person with cancer needs to receive very high doses of chemotherapy, a PBPC transplant can help recovery of blood cells after treatment. Progenitor cells from the blood are collected before the high doses of chemotherapy and then given back afterward. The STEMGEN® (ancestim) you will be taking, together with NEUPOGEN® (filgrastim), another blood cell growth factor, will help your bone marrow make extra progenitor cells for collection.

STEMGEN® (ancestim) is the BioVitrum AB product name for Stem Cell Factor. Stem Cell Factor is a blood cell growth factor that is naturally produced in the body in small amounts to make progenitor cells (also known as stem cells) grow. Progenitor cells are the very early forms of blood cells that mature to become red blood cells, white blood cells, and platelets. Progenitor cells are made in the bone marrow and can be found in the bone marrow and in the blood.

STEMGEN® for people undergoing PBPC transplants
You will be given STEMGEN® and NEUPOGEN® injections for several days in a row to increase the number of progenitor cells in your blood. These progenitor cells will be removed from your blood on certain days of treatment (normally daily, beginning day 5 for up to 5 days) using a procedure called apheresis (ay-fuh-ree-sis). The cells collected will be frozen and stored, and then thawed and returned to your bloodstream (transplanted) after you have had chemotherapy treatment for your cancer. The transplanted cells will help to restore your blood counts after chemotherapy. By using STEMGEN® with NEUPOGEN®, higher numbers of progenitor cells can be collected with fewer apheresis procedures.

What are the possible side effects of STEMGEN® ?
STEMGEN® is given with another drug called NEUPOGEN®. Both STEMGEN® and NEUPOGEN® are given as separate injections under the skin (subcutaneous) but at different injection sites. You will be asked to remain in the hospital for observation for about 1 hour to be sure you do not get an allergic reaction to STEMGEN®. If you think you are having an allergic reaction, contact the staff where you are, immediately.

Allergic reactions may be early or late occurring. You are asked to stay in the hospital for about 1 hour so that you can be treated immediately should you have an early occurring reaction. In order to protect against the possibility of a delayed (late occurring) allergic reaction to STEMGEN® occurring after you have left the hospital, it is very important that you take the premedications (antihistamines and inhaler) prescribed to you by your doctor exactly as instructed. If you forget to take your premedications on time, it is important to take them immediately and

then resume the correct schedule. If you have forgotten to take your premedications and are about to receive STEMGEN®, tell your doctor before you are given STEMGEN®.

A small number of people (about 5 in 100) experience allergic reactions which could become more serious and might be life-threatening if not treated promptly. These reactions may include widespread hives and/or throat tightness or wheezing. Occasionally, these reactions have included swelling around the face, tongue or throat, fast heart beat, or low blood pressure. Allergic reactions can happen anytime but usually occur within 12 hours of taking STEMGEN® and can be treated with antihistamines, steroids, or other medications. If you think you may be having an allergic reaction to STEMGEN®, call your doctor immediately. If you have a history of severe allergic reactions (including hives all over the body, wheezing, or difficulty swallowing), asthma, recurring hives, or facial swelling, you may be more likely to have allergic side effects, and should discuss this with your doctor before taking STEMGEN®.

In patients who are adequately screened for allergy history and are premedicated, STEMGEN® is generally well-tolerated, although there are some side effects. Nearly all people experience redness, itching, or swelling at the site of injection of STEMGEN®. Over a few days, some people's skin may darken at the site of injection. This will disappear, but may take several weeks or months. Many patients may also experience bone pain. Clinical studies show that approximately half of the patients administered STEMGEN® experience bone pain ranging from mild-to-moderate in severity. If you experience bone pain while receiving STEMGEN®, discuss this side effect with your doctor. Some patients experience mild cough, or mild shortness of breath. Some patients have skin redness or itchiness in places other than the site of injection.

Please note that the information included in this leaflet is not intended to include all known or possible effects of STEMGEN®. You should discuss any questions with your doctor.

Premedications for STEMGEN®

In order to protect against the possibility of an allergic reaction to STEMGEN®, it is very important that you take the premedications (antihistamines and inhaler) prescribed to you by your doctor exactly as instructed. Keep your premedications with you at all times, even when traveling. If you forget to take your premedications on time, it is important to take them immediately, and then to resume the correct schedule.

What should I do if I have an allergic reaction?

If you think you are having an allergic reaction, contact your doctor immediately. You should tell your doctor the time you last took your premedications. Your doctor will decide if you should take your antihistamines and/or inhaler to treat the reaction. Therefore, you should keep your premedications with you at all times. If your reaction is very severe and you are having difficulty breathing or swallowing, contact emergency medical personnel immediately.

PHARMACOLOGY

General

Receptors for SCF are found on a range of early to more mature hematopoietic progenitor cells, as well as mast cells, melanocytes, and germ cells.[2,5] In vitro, recombinant SCF as a single agent shows little colony-stimulating activity on hematopoietic progenitor cells. However, it synergistically increases the colony-forming or stimulatory activity of numerous hematopoietic growth factors, including granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, erythropoietin, megakaryocyte growth and development factor, and interleukin-2.[2,3] In vivo, recombinant SCF administration at high doses has been shown to stimulate multiple hematopoietic lineages in mice, dogs, and primates.[2,3,6] At lower doses, it synergizes with recombinant G-CSF to mobilize PBPC capable of rescuing mice, dogs, and primates from otherwise lethal irradiation.[2,3,7] 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.[2,3] 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.[1]

Clinical Experience: Response to STEMGEN® (ancestim)

STEMGEN®, administered in conjunction with NEUPOGEN® (filgrastim), has been shown to be safe and effective in increasing apheresis PBPC yields in patients with breast cancer, lymphoma, multiple myeloma, and ovarian cancer in both cytokine-alone and chemotherapy-based PBPC mobilization regimens. In several studies, this increase in PBPC yield was more sustained across the days of apheresis and was demonstrated to reduce the number of apheresis procedures required to collect a target number of PBPC.

In the phase 3 controlled clinical trial, breast cancer patients were randomized to receive either 20 mcg/kg/day STEMGEN® SC in combination with 10 mcg/kg/day NEUPOGEN® (n = 101) or 10 mcg/kg/day NEUPOGEN® alone (n = 104). In this study, the benefits of STEMGEN® therapy were shown to include a reduction in the number of aphereses required to collect a target number of PBPC and an increase in the proportion of patients from whom an optimal PBPC harvest could be obtained. As expected for patients apheresed to the same target cell yield,

there was no difference between the treatment groups in hematopoietic recovery following high-dose chemotherapy and infusion of the collected PBPC.

The phase 3 study was conducted in stage II, III, or IV breast cancer patients who had received a median of five cycles of prior chemotherapy. Patients receiving STEMGEN® were prophylactically medicated with H_1 and H_2 antihistamines, an inhaled bronchodilator, and pseudoephedrine. On day 5 of cytokine administration, apheresis was initiated. Apheresis and cytokine administration were continued daily until the target of 5 x 10^6 $CD34^+$ cells/kg (actual body weight) had been collected, up to a maximum of five 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 x 10^6 $CD34^+$ cells/kg was correlated with a high probability of rapid platelet recovery (by day14) and a low probability of delayed platelet recovery (≥ 28 days).[4]

Following PBPC collection, patients who had at least 1 x 10^6 $CD34^+$ cells/kg collected underwent high-dose chemotherapy with a modified STAMP I regimen.[8] Infusion of PBPC began 2 days following the last dose of chemotherapy. NEUPOGEN® (10 mcg/kg/day) was initiated on the first day of PBPC infusion, and all patients were followed for recovery of neutrophils to ≥ 0.5 x 10^9/L and platelets ≥ 20 x 10^9/L. A total of 204 patients received at least one dose of cytokine and were evaluated for safety, and 203 patients had at least one apheresis performed and were evaluated for efficacy.

Treatment with STEMGEN® plus NEUPOGEN® caused a sustained mobilization of PBPC resulting in greater $CD34^+$ cell collections and a greater proportion of patients reaching the target yield (63%) compared to treatment with NEUPOGEN® alone (47%).This improved $CD34^+$ cell mobilization 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 four apheresis procedures, while patients receiving NEUPOGEN® alone required a median of greater than or equal to six aphereses (ie, less than 50% of NEUPOGEN®-treated patients reached the collection target in five aphereses). Results of an evaluable subset of patients (n = 175) were similar; evaluable patients receiving STEMGEN® plus NEUPOGEN® reached ≥ 5 x 10^6 $CD34^+$ cells/kg in a median of three aphereses, compared to a median of greater than or equal to six aphereses for evaluable patients receiving NEUPOGEN® alone (p = 0.009).

Median days to engraftment of neutrophils and platelets following high-dose chemotherapy were similar between patients receiving STEMGEN® plus NEUPOGEN® and those receiving NEUPOGEN® alone: 10 and 9 days, respectively, for neutrophil recovery and 11 days for transfusion-independent platelet recovery. STEMGEN® was generally well-tolerated when given SC at a

dose of 20 mcg/kg/day for up to 9 consecutive days (see ADVERSE REACTIONS).

In the phase 3 study, the proportion of patients who were either mobilization or engraftment failures, that is: 1) failed to reach, in 5 aphereses, a minimal number of $CD34^+$ cells (1 x 10^6/kg) to allow high-dose chemotherapy with PBPC support, or 2) experienced delayed platelet recovery to 20 x 10^9/L (≥ 28 days), was lower for patients receiving STEMGEN® plus NEUPOGEN®, compared to those receiving NEUPOGEN® alone (3.5% vs 7.4%). In the 219 patient phase 1/2 breast cancer study which utilized three fixed aphereses, 12% of patients treated with 20 mcg/kg/day STEMGEN® plus NEUPOGEN® and 19% of patients treated with NEUPOGEN® alone were either mobilization or engraftment failures.

Several additional randomized, controlled studies also support the efficacy of STEMGEN® in breast cancer, lymphoma, multiple myeloma, and ovarian cancer. In studies using cytokine-alone mobilization, apheresis usually commenced on day 5. In studies of chemotherapy plus cytokine mobilization, apheresis typically commenced when the WBC count rose through 4 x 10^9/L following the chemotherapy-induced nadir (usually day 9 to 18). As shown in the table below, the addition of STEMGEN® to NEUPOGEN® resulted in increased apheresis yields of $CD34^+$ cells, increased numbers of patients with apheresis harvests ≥ 5 x 10^6 $CD34^+$ cells/kg, and reduced apheresis requirements to collect 5 x 10^6 $CD34^+$ cells/kg. A meta-analysis across all PBPC studies showed that there was a highly significant improvement ($p < 0.0001$) in each of these efficacy parameters for patients receiving STEMGEN® plus NEUPOGEN® compared to patients receiving NEUPOGEN® alone. Data from the phase 3 and supportive studies are summarized in the following table.

Type of Malignancy (Degree of Prior Therapy)	No. of Pts.	Mobilization Regimen	STEMGEN® Plus NEUPOGEN® Daily Dosage[a] (mcg/kg/day)	Fold Increase in Median $CD34^+$ Cells Collected per Apheresis (10^6/kg)	Reduction in Median No. Aphereses to Collect 5 x 10^6 $CD34^+$ cells/kg
Randomized, controlled trials using 20 mcg/kg/day STEMGEN®					
NHL and Hodgkin's Disease[8] (extensive)	107	Cytokine-alone	STEMGEN® (20) NEUPOGEN® (10)	1.5	g
Breast Cancer[9] (moderate)	205	Cytokine-alone	STEMGEN® (20) NEUPOGEN® (10)	1.7	≥ 2
Multiple Myeloma[10] (moderate)	102	Chemotherapy[b] and Cytokine	STEMGEN® (20) NEUPOGEN® (5)	2.4	1
Exploratory studies using 20 mcg/kg/day STEMGEN®					
Multiple Myeloma[11] (extensive)	39	Cytokine-alone	STEMGEN® (20) NEUPOGEN® (10)	1.2	g
NHL and Hodgkin's Disease (extensive)	53	Chemotherapy[c] and Cytokine	STEMGEN® (20) NEUPOGEN® (5)	2.3	g
Dose finding studies using doses of 5 to 30 mcg/kg/day STEMGEN®					
Ovarian Cancer[12] (none)	48	Chemotherapy[d] and Cytokine	STEMGEN® (5 to 20) NEUPOGEN® (5)	2.9[e]	≥ 1[e]
Breast Cancer[13] (none)	62	Cytokine-alone	STEMGEN® (5 to 15) NEUPOGEN® (12)	1.8[e]	1[e]
Breast Cancer[4] (moderate)	219	Cytokine-alone	STEMGEN® (5 to 30) NEUPOGEN® (10)	2.3[f]	≥ 1[r]
Non-Hodgkin's Lymphoma[14] (NHL) (extensive)	23	Cytokine-alone	STEMGEN® (5 to 20) NEUPOGEN® (10)	6.4[e]	e,g

[a] All STEMGEN® doses tested in each study are listed, including those different from the recommended dose.
[b] Cyclophosphamide (4 g/m^2)
[c] Dexa-BEAM[15]:Dexamethasone 8 mg, days 1 to 10; BCNU 60 mg/m^2, day 2; Etoposide 75 mg/m^2, days 4 to 7; Ara-C 100 mg/m^2, days 4 to 7; Melphalan 20 mg/m^2, day 3
[d] Cyclophosphamide (3 g/m^2)
[e] All STEMGEN® dose groups are combined.
[f] STEMGEN® 20 mcg/kg/day plus NEUPOGEN® x 7 days (n = 35) versus NEUPOGEN® alone (n = 55).
[g] An insufficient number of patients reached the target. Therefore this value could not be calculated.

In clinical trials of STEMGEN® in combination with NEUPOGEN® for the mobilization of PBPC, NEUPOGEN® was administered to patients at 5 to 10 mcg/kg/day after infusion of the collected cells until a sustainable neutrophil count (> 0.5 x 10^9/L) was reached. The rate of neutrophil and platelet recovery following PBPC infusion in the absence of NEUPOGEN® post-transplantation was not studied in these clinical trials. These studies were not designed to assess effects of STEMGEN® on tumor growth or patient survival, however, response rates and survival were similar between treatment groups.

TOXICOLOGY

Ancestim was administered to nonhuman primates as part of the preclinical toxicology program which included single-dose acute, repeated-dose subacute, and subchronic studies. Single-dose and 21-day repeated-dose administration of ancestim by the SC route resulted in no deaths or other significant toxicity in monkeys at doses of 12,000 mcg/kg (single-dose) or 6000 mcg/kg/day, respectively. In a subchronic (13 week) study in monkeys, 4 of 12 monkeys treated with the highest dose of ancestim (6000 mcg/kg/day SC) died or were euthanized moribund. The mortality in these monkeys was considered related to ancestim treatment, although no consistent etiology for the deaths could be established. The pathologic findings in these monkeys included skin papules and vesicles comprised of numerous mast cells, vascular lesions with multifocal edema, or numerous vacuolated cells in the liver, lymph nodes, and spleen.

In repeated-dose studies in monkeys, changes observed were generally attributable to the expected pharmacological actions of ancestim. There were dose-dependent increases in PBPC, WBC, RBC, reticulocytes, bone marrow proliferation, tissue mast cells, and skin pigmentation. Histopathologic examination of the liver and spleen revealed evidence of extramedullary hematopoiesis. A dose-dependent decrease in serum iron was observed in the 13-week study, and may reflect increased erythropoiesis. These changes were reversible following discontinuation of treatment.

The combination of ancestim (100 and 1000 mcg/kg/day) and filgrastim (10 and 100 mcg/kg/day) given SC to cynomolgus monkeys for 28 days resulted in no unexpected toxicity. The principal findings were consistent with the pharmacologic actions of these agents. The only noted additive effects of the combined treatment were increases in the degree of bone marrow hypercellularity and of extramedullary hematopoiesis in the liver and spleen. These findings were reversible following a 2-week recovery period.

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 mcg/kg (baboons) or 6000

mcg/kg (monkeys) were administered by rapid IV injection. No such reactions were observed in primates administered SC ancestim in the toxicology studies noted above. These mast cellmediated reactions were characterized by hypotension and bronchoconstriction. Angioedema, wheezing, rales, vomiting, and piloerection were observed infrequently. 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.

Reproductive studies in pregnant and nursing monkeys have shown that ancestim was not associated with lethal, teratogenic, or behavioral effects on fetuses when administered by daily SC injection during the period of organogenesis at dose levels up to 1000 mcg/kg/day, or during the prenatal and postnatal periods at dose levels up to 300 mcg/kg/day.

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