

Molgramostim

Macrogen™

1. GENERIC NAME

Molgramostim

2. DESCRIPTION

Molgramostim is recombinant human granulocyte macrophage-colony stimulating factor (rHuGM-CSF) containing 127 amino acids with a molecular weight of 14,477 Daltons. Molgramostim is produced by a strain of *Escherichia coli* (*E.coli*) bearing a genetically engineered plasmid containing the human GM-CSF gene. Molgramostim is non-glycosylated and has isoleucine in position 100 (thr100 is replaced with ile 100). The protein is expressed in the periplasmic space of the bacterium and hence does not carry a formyl methionine at the N-terminus.

3. COMPOSITION

Each single dose vial of Macrogen™ (Molgramostim) contains 4.4×10^6 IU (equivalent to 400 micrograms) of molgramostim as sterile lyophilized powder for injection after reconstitution as a solution for intravenous or subcutaneous administration. See table below for quantitative composition of each lyophilized single dose vial.

	Each single dose vial of Macrogen™ contains
Molgramostim (GM-CSF)	400 mcg
Mannitol	50 mg
Anhydrous citric acid	0.28 mg
Sodium phosphate	2.6 mg
Macrogol 4000	0.1 mg
Human serum albumin	1.0 mg

4. INDICATIONS

Molgramostim is indicated:

In patients receiving myelosuppressive therapy (cytotoxic chemotherapy for non-myeloid malignant disease) to reduce the severity of neutropenia, thereby reducing the risk of infection and allowing better adherence to the chemotherapeutic regimen;

In patients undergoing autologous or syngeneic bone marrow transplantation to accelerate myeloid recovery (molgramostim does not improve overall survival or increase time to relapse).

5. DOSE AND METHOD OF ADMINISTRATION

Molgramostim must be reconstituted before administration. Molgramostim dosing regimens vary according to the indication for therapy. The maximum daily dose should not exceed 10mcg/kg body weight.

The recommended dosage regimens are:

5.1. Cancer chemotherapy: 5 to 10mcg/kg per day administered subcutaneously. Treatment should be initiated 24 hours after the last dose of chemotherapy and continued for 7 to 10 days. Dosing may be initiated at 5mcg/kg a day.

5.2. Bone marrow transplantation (BMT): 10mcg/kg per day administered by i.v. infusion over 4 to 6 hours, beginning the day after BMT and being continued until the absolute neutrophil count (ANC) is $\geq 1000/\text{mm}^3$. The maximum duration of treatment is 30 days.

6. USE IN SPECIAL POPULATIONS

6.1. Use during pregnancy and lactation: Safety of molgramostim for use in human pregnancy has not been established. Animal studies have shown reproductive toxicity.

In the absence of clinical data in pregnancy, the therapeutic benefit to the patient must be weighed against potential risks to the progress of pregnancy.

It is not known whether molgramostim is excreted in human milk. However, because of the potential for adverse effects in infants, nursing is not recommended in women receiving molgramostim.

Studies in humans to determine effects of molgramostim on fertility have not been undertaken.

6.2. Paediatric use: The safety of molgramostim has been demonstrated in a limited number of patients below the age of 18 years.

6.3. Use in the elderly: There are no apparent differences in safety of molgramostim between elderly and non-elderly patients.

6.4 Use in kidney and/or liver failure: In the absence of relevant experience, molgramostim should not be administered in severe cases.

7. CONTRAINDICATIONS

Molgramostim is contraindicated in patients with a history of hypersensitivity to molgramostim or any component of the injectable formulation. Molgramostim should not be used in patients with myeloid malignancies.

8. WARNINGS AND PRECAUTIONS

Molgramostim should be used under the supervision of a physician experienced in the treatment of oncologic and haematopoietic disorders or infectious diseases. The first dose of molgramostim should be administered under close medical supervision.

There have been rare reports of acute severe, life-threatening hypersensitivity reactions, including anaphylaxis, angio-oedema or bronchoconstriction in patients receiving molgramostim. If such reactions occur, molgramostim should be withdrawn immediately and not re-introduced.

Molgramostim has been associated infrequently with pleuritis, pleural effusion, pericarditis and/or pericardial effusion. If such reactions occur, molgramostim should be withdrawn.

Patients with pre-existing pulmonary disease may be predisposed to decreased pulmonary function and dyspnoea, and should be monitored closely when being treated with molgramostim.

In clinical trials, adverse events reported with initiation of dosing were mostly mild to moderate in severity, and included rigors, dyspnoea, fever, nausea, vomiting, non-specific chest pain, asthenia, hypotension or flushing. These symptoms, which infrequently required withdrawal of molgramostim, were managed symptomatically.

In a few isolated instances, autoimmune disease developed or was exacerbated during rHuGM-CSF therapy; therefore, when administering molgramostim to patients with a history of autoimmune disease, this should be considered.

9. DRUG INTERACTIONS

Since dosing with molgramostim has been associated with a decrease in serum albumin, drugs that are highly bound to serum albumin may require dosage adjustment. Although with molgramostim no adverse drug interaction has been reported, the possibility of a drug-drug interaction cannot be excluded completely.

10. UNDESIRABLE EFFECTS

Since many of the undesirable effects reported during molgramostim clinical trials are often associated with underlying or concurrent diseases or their treatment, the causal relationship of these effects to molgramostim cannot be definitively determined. Most adverse reactions observed were mild or moderate in severity. Rarely were they severe or life-threatening.

The most frequently reported undesirable effects across all indications were fever, nausea, dyspnoea, diarrhoea, rash, rigors, injection site reaction (with s.c. administration), vomiting, fatigue, anorexia, musculoskeletal pain and asthenia.

Less frequently reported events include: non-specific chest pain, stomatitis, headache, increased sweating, abdominal pain, pruritus, dizziness, peripheral oedema, paraesthesia and myalgia.

Serious reactions, which occurred rarely in clinical trials, include: anaphylaxis, bronchospasm, cardiac failure, capillary leak syndrome, cerebrovascular disorders, confusion, convulsions, hypotension, cardiac rhythm abnormalities, intracranial hypertension, pericardial effusion, pericarditis, pleural effusion, pulmonary oedema and syncope.

11. OVERDOSE

Accidental overdosing has not been reported with molgramostim. However, in some patients receiving therapeutic doses of 20 or 30mcg/kg per day, tachycardia, hypotension and a flu-like syndrome have been observed; these symptoms abated quickly upon symptomatic treatment

12. PHARMACOKINETIC PROPERTIES

Studies in rats showed that radioactivity was extensively distributed following i.v. administration of ¹²⁵I-rHuGM-CSF. The drug appeared to be rapidly metabolised and excreted. The pharmacokinetic profiles of molgramostim were similar in monkeys, healthy male volunteers and patients. After s.c. doses of 3, 10 or 20mcg/kg and after i.v. doses of 3 to 30 mcg/kg, increases in the total area under curve (AUC) were dose-related. Maximum molgramostim serum concentrations were reached in 3 to 4 hours after s.c. administration. Molgramostim had an elimination half-life of 1 to 2 hours after i.v. administration and of 2 to 3 hours after s.c. administration. The slightly longer half-life observed after s.c. administration is probably due to prolonged absorption from the injection site.

13. LABORATORY MONITORING

In all patient groups, the most frequently occurring changes in laboratory values were decreased platelet count, decreased haemoglobin level, and decreased serum albumin level. The causal relationship of these changes to molgramostim cannot be determined definitively.

Increased eosinophil counts (absolute and percent) have also been observed.

The frequency of antibodies that bind to molgramostim, measured by enzyme-linked immuno sorbent assay (ELISA) and bioassay was determined to be 1% post treatment. No loss of efficacy of molgramostim was evident in these patients.

14. SHELF-LIFE

Macrogen™ (Molgramostim) sterile powder, packaged in a Type-I glass vial with halobutyl rubber closure and aluminium seal, is stable for 24 months when stored at 2 to 8°C. After reconstitution with sterile water for injection, Molgramostim solution can be used for 24 hours when refrigerated at 2 to 8°C. Unused Molgramostim solution should be discarded

15. PACKAGING INFORMATION

One single dose vial (4.4 x 10⁶ IU) containing molgramostim in sterile lyophilized powder form. The contents of the vial have to be reconstituted with sterile water for injection. Add 1.0 ml of sterile water for injection to the vial containing the molgramostim powder. Shake the vial gently until the powder has dissolved completely. The solution will be clear and colorless. This can be used for subcutaneous administration. For intravenous administration, reconstitute the required number of vials each with 1.0 ml of sterile water for injection. The reconstituted molgramostim must then be transferred to a 20-100ml infusion bag or bottle containing physiological saline or 5% glucose. The number and strength of lyophilized powder vials must be determined in such a way that the above infusion admixture solution contains a final concentration of molgramostim of not less than 7mcg/ml. The resulting infusion solution is stable for at least 24 hours when kept in the refrigerator at 2-8°C. For intravenous infusion the use of a low protein binding 0.2 µm filter is recommended. Inspect the reconstituted solution for discoloration or particulate matter prior to administration.

Each vial is packed in individual cartons.

16. STORAGE AND HANDLING INSTRUCTIONS.

Store at 2°C to 8°C, protected from light. Refrigerate, but do not freeze.

Medicine: Keep out of reach of children.

Manufactured and Marketed in India by:
Zenotech Laboratories Limited
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