Brand Name: GenePlat Injection
Chemical name: Recombinant Human Interleukin-11
Active ingredient: Recombinant Human Interleukin-11,0.75mg,1.5mg & 3mg
with inactive ingredients of Glycine 23 mg, Na2HPO4 0.85 mg, NaH2 PO4 0.48mg per vial.
Appearance:
White or pale yellowish powder, soluble in water.
Pharmacology and Toxicology
Pharmacology:
Recombinant Human Interleukin-11, produced by recombinant DNA technology, is a thrombopoietic growth factor that directly stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells and induces megakaryocyte maturation resulting in increased platelet production, so as to elevate platelet count without significant change of platelet function.
Pre-clinical studies have shown that mature megakaryocytes which develop during in vivo treatment with rhIL-11 are ultra-structurally and functionally normal and possessed a normal life span.
Toxicology:
Safety Pharmacology:
IL-11 has shown to have non-hematopoietic activities in animals including the regulation of intestinal epithelium growth (enhanced healing of gastrointestinal lesions), the inhibition of adipogenesis, the induction of acute phase protein synthesis, inhibition of pro-inflammatory cytokine production by macrophages, and the stimulation of osteoclastogenesis and neurogenesis.
Toxicity of Repetitive Administration:
Continuous dosage (2 to 13 weeks) in nonhuman primates produced joint capsule and tendon fibrosis and periosteal hyperostosis. The relevance of these findings to human is unclear.
Genetic Toxicity:
In vitro studies have shown that rhIL-11 is not mutagenic.
Reproduction Toxicity:
Although prolonged estrus cycles have been noted at 2 to 20 times the human dose, no effects on fertility have been observed in rats treated with rhIL-11 at doses up to 1000μg/kg/day.
The studies on fertility and early embryonic development of rats and organogenesis of rats and rabbits have shown that parental toxicity was observed when rhIL-11 was given at dose of 2~20 times the human dose (>100μg/kg/day) in the rat and at 0.02~2.0 times of human dosage (>1μg/kg/day) in the rabbit. Findings in pregnant rats consisted of transient hypoactivity and dyspnea after administration (maternal toxicity), as well as prolonged estrus cycle, increased early embryonic deaths and decreased numbers of live fetuses. In addition, low fetal body weights and a reduced number of ossified sacral and caudal vertebrae (i.e. retarded fetal development) occurred in rats at 20 times the human dose without long-term abnormality of behavior or development. Findings in pregnant rabbits consisted of decreased fecal/urine eliminations as well as decreased food consumption, body weight loss, abortion, increased embryonic and fetal deaths, and decreased numbers of live fetuses, without observation of teratogenic effects. There are no adequate and well-controlled studies of rhIL-

11 in pregnant women. rhIL-11 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known if rhIL-11 is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rhIL-11, a decision should be made whether to discontinue nursing or to discontinue rhIL-11, taking into account the importance of the drug to the mother.

Carcinogenesis:

No studies have been performed to assess the carcinogenic potential of rhIL-11. In vitro, rhIL-11 did not stimulate the growth of tumor colony-forming cells harvested from patients with a variety of human malignancies.

Pharmacokinetics:

In a study in which a single 50μg/kg subcutaneous dose was administered, the peak serum concentration (Cmax)of 17.4+5.4ng/ml was reached at 3.2+2.4hrs (Tmax) following dosing. The terminal half-life was 6.9+1.7hrs. In a second study in which single 75μg/kg subcutaneous and intravenous dose were administered, the pharmacokinetic profiles were similar between healthy men and women. The bioavailability of rhIL-11 under subcutaneous administration was above 80%, and accumulation in vivo or impaired clearance rate was not observed.

In rats, radio-labeled rhIL-11 was rapidly cleared from the serum and distributed to highly perfused organs. The kidney was the primary route of elimination. The amount of intact rhIL-11 in urine was low, indicating the molecule was metabolized before excretion.

Indications:

GenePlat is indicated for the treatment of Grade III and IV thrombocytopenia after chemotherapy on solid tumor and non-myeloid leukemia; For patients with solid tumor or non-myeloid leukemia, if the former chemotherapy course results in Grade III or IV thrombocytopenia (platelet count<5x109/L), GenePlat is recommended before the next chemotherapy in order to reduce hemorrhage resulting from thrombocytopenia and the need of platelet transfusion. If necessary, patients with thrombocytopenia can administer rhG-CSF concomitantly with GenePlat.

Dosage and administration:

According to the results of clinical studies of GenePlat, the recommended dosage is 50μg/kg/day, administered subcutaneously 24~48 hours after chemotherapy or observation of thrombocytopenia (reconstitute with 1ml sterile water for injection), once daily. The course of treatment is normally 7~14 days. Administration should be timely discontinued when platelet count recovers.

Adverse Reactions:

Clinical studies reported:

Apart from the adverse reactions resulting from chemotherapy, most adverse reactions of rhIL-11 were mild or moderate in severity and rapidly reversible after discontinuation of rhIL-11 dosing.

Above 10% patients had experienced the following adverse reactions during the observation period: asthenia, pain, chills, abdominal pain, infection, anorexia, constipation, dyspepsia, ecchymosis, myalgia, bone pain, nervousness, and alopecia. The incidence of most adverse events was similar between rhIL-11 and placebo groups, whereas the adverse reactions with higher incidence in the rhIL-11 group are listed as follows.

Systemic Reactions: edema, headache, fever, neutropenic fever;
Cardiovascular System Reactions: tachycardia, vasodilatation, palpitations, syncope, atrial fibrillation and atrial flutter;
Digestive System Reactions: nausea, vomiting, mocusitis, diarrhea, oral moniliasis;
Nervous System: dizziness, insomnia;
Respiratory System: dyspnea, rhinitis, cough increased, pharyngitis, pleural effusions;
Others: rash, conjunctival congestion, short-lived blurred vision.
In addition, the following adverse events also occurred more frequently in cancer patients receiving rhIL-11 than in those receiving placebo: amblyopia, paresthesia, dehydration, skin discoloration, exfoliative dermatitis, and eye hemorrhage; a statistically significant association of rhIL-11 to these events has not been established. Other than a higher incidence of severe asthenia in rhIL-11 treated patients (10 [14%] in rhIL-11 patients versus 2 [3%] in placebo patients), the incidence of severe events was comparable in the rhIL-11 and placebo treatment groups.
Two patients with cancer treatment in rhIL-11 experienced sudden death which the investigator considered possibly or probably related to rhIL-11. Both deaths occurred in patients with severe hypokalemia
(<3.0 mEq/L) who had received high doses of ifosfamide and were receiving daily doses of a diuretic. Therefore, it is not determined if the sudden deaths were relevant to rhIL-11.
The most common laboratory abnormality reported in patients in clinical trials was a decrease in hemoglobin concentration pre-dominantly as a result of expansion of the plasma volume. The increase in plasma volume is also associated with a decrease in the serum concentration of albumin and several other proteins (e.g., transferring and gamma globulins). A parallel decrease in calcium without clinical effects has been documented.
After daily SC injections, treatment with rhIL-11 resulted in a two-fold increase in plasma fibrinogen. Other acute-phase proteins also increased. These protein levels returned to normal after dosing with rhIL-11 was discontinued. Von Willebrand factor (vWF) concentrations increased with a normal multimer pattern in healthy subjects receiving rhIL-11.
Contraindication:
There was a report that rhIL-11 caused serious hypersensitivity. Therefore, GenePlat is contraindicated in patients with a history of hypersensitivity to rhIL-11 or any component of the product. Any patient with a history of hypersensitivity to blood derived products and other biological products expressed by yeast should use GenePlat with caution.
Warnings/ Precautions:
1. GenePlat should be used after the completion of chemotherapy rather than during the period of chemotherapy course.
2. The routine hemogram test should be checked in the course of using GenePlat every other day, platelet count should be closely observed. The dosing should be discontinued when platelet count is recovered above 100 x 109 /L.
3.For patients with organic cardiopathy especially congestive heart failure or history of atrial fibrillation or atrial flutter,GenePlat should be used with great caution.
4.Capillary effusion syndrome, e.g. weight, edema, dropsy of serous cavity should be monitored in the course of using GenePlat

5.GenePlat is only prescribed by doctors or used under doctor's direction.

Dosage for Pregnancy or Nursing Mothers:

There are no adequate and well-controlled studies of rhIL-11 in pregnant women, GenePlat should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known if rhIL-11 is excreted in human milk, therefore GenePlat should be used cautiously in nursing mothers.

Pediatric Use:

A safe and effective dose of rhIL-11 has not been established in children.

Geratic use:

Usually consistent with dosage for adults.

Drug Interactions:

When G-CSF was used concomitantly with rhIL-11, no adverse effect has been found of rhIL-11 on the activity of G-CSF or G-CSF on the activity of rhIL-11. Drug interactions between rhIL-11 and other drugs have not been fully evaluated. Based on in vitro and non-clinical in vivo evaluations of rhIL-11, drug interactions with known substrates of P450 enzymes would not be predicted.

Overdosage:

Overdosage of rhIL-11 could result in some toxic and side effects, such as retention of water and sodium, atrial fibrillation etc. The dosage should be reduced or discontinued and the patients should be closely observed.

How Supplied?:

Geneplat is supplied as follows:

0.75mg/vial, 1.5mg/ vial, 3mg/ vial

Storage:

Protect from light, store at 2-8oC(36oF-46oF). DO NOT FREEZE. Reconstituted GenePlat can be stored in vial either at 2-8oC(36oF-46oF) or at room temperature up to 25oC(77oF) and must be used within 3 hours of reconstitution. Do not use when the date is beyond the expiry date noted on the package.

Package:

1 vial/box

Validity:

30 months