Professional Information for PEGYLASTIN

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

PEGYLASTIN injection

COMPOSITION

Each pre-filled syringe or pre-filled injector contains 6 mg pegfilgrastim in 0,6 mL (10 mg/mL) solution for injection.

Pegfilgrastim is composed of filgrastim (recombinant methionyl human granulocyte colony-stimulating factor (G-CSF)) with a 20 kDa polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue.

Inactive ingredients: Polysorbate 20, sorbitol and water for injection.

Contains sugar (30 mg sorbitol per 0,6 mL).

CATEGORY AND CLASS

A 8.5 Medicines acting on blood and haemopoietic system – others

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Human granulocyte colony-stimulating factor (G-CSF) is a glycoprotein produced in *Escherichia coli*, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim is a covalent conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kDa polyethylene glycol (PEG) molecule bound to the N-terminal methionine residue of the 175-amino acid G-CSF. Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in

monocytes and/or lymphocytes. Neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. G-CSF has shown *in vitro* stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells *in vitro,* and similar effects may be seen on some non-myeloid cells *in vitro*.

Pharmacokinetic properties:

The elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance, which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declines rapidly at the onset of neutrophil recovery. The circulating $t_{½}$ of pegfilgrastim is longer than that of filgrastim, allowing for more sustained duration of action and less frequent dosing.

INDICATIONS

PEGYLASTIN is indicated to reduce the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

CONTRAINDICATIONS

PEGYLASTIN is contraindicated in patients with known hypersensitivity to pegfilgrastim, filgrastim, *Escherichia coli*-derived proteins, or to any inactive ingredients of PEGYLASTIN (see COMPOSITION).

WARNINGS AND SPECIAL PRECAUTIONS

Hypersensitivity

Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with PEGYLASTIN. Permanently discontinue PEGYLASTIN in

patients with clinically significant hypersensitivity. Do not administer PEGYLASTIN to patients with a history of hypersensitivity to pegfilgrastim or filgrastim. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days.

Immunogenicity

There is a potential for immunogenicity. Rates of generation of antibodies against pegfilgrastim is generally low. Binding antibodies do occur; however, they have not been associated with neutralising activity at present.

Splenomegaly and splenic rupture

There have been isolated cases of splenic rupture following administration of granulocyte colony-stimulating factors, such as PEGYLASTIN. Some of these isolated cases have resulted in a fatal outcome. A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Sickle cell anaemia:

High leucocyte counts are disadvantageous prognostic factors in patients with sickle cell anaemia. Therefore, healthcare providers should exercise caution when administering PEGYLASTIN in patients with sickle cell disease or trait, should monitor appropriate clinical parameters and laboratory status, and be attentive to the possible association of PEGYLASTIN with splenic enlargement and vaso-occlusive crisis.

Leucocytosis:

White blood cell (WBC) counts of 100 x 10^9/L or greater have been observed in less than 1 % of patients receiving PEGYLASTIN. No adverse events directly attributable to this degree of leucocytosis have been reported. Such elevation in white blood cells is transient, typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of PEGYLASTIN. Consistent with the clinical effects and the potential for leucocytosis, a WBC count should be performed at regular intervals during therapy. If leucocyte counts exceed 50 x 10^9/L after the expected nadir, PEGYLASTIN should be discontinued immediately.

The safety and efficacy of PEGYLASTIN for the mobilisation of blood progenitor cells in patients or healthy donors have not been adequately evaluated.

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging findings. This should be considered when interpreting bone-imaging results.

Pulmonary adverse events:

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk (see SIDE EFFECTS).

The onset of pulmonary signs such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of adult respiratory distress syndrome (ARDS). In such circumstances PEGYLASTIN should be discontinued at the discretion of the healthcare provider and the appropriate treatment given.

Treatment should be withdrawn in patients who develop signs of pulmonary infiltrates. Transient positive changes in bone imaging findings have occurred with growth factor therapy and should be considered when interpreting results. Bone density should be monitored in patients with osteoporosis who are receiving long-term treatment with PEGYLASTIN.

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving PEGYLASTIN. Generally, symptoms of glomerulonephritis resolved after dose reduction or withdrawal PEGYLASTIN. Urinalysis monitoring is recommended.

Capillary leak syndrome:

Capillary leak syndrome has been reported after G-CSF administration and is characterised by hypotension, hypalbuminaemia, oedema and haemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care (see SIDE EFFECTS).

Thrombocytopenia and anaemia:

Treatment with PEGYLASTIN alone does not preclude thrombocytopenia and anaemia because full dose myelosuppressive chemotherapy is maintained on the prescribed schedule. Regular

monitoring of platelet count and haematocrit is recommended.

Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

Administration of PEGYLASTIN in combination with 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression.

PEGYLASTIN is incompatible with sodium chloride solutions.

The safety and efficacy of PEGYLASTIN have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukaemia, and in patients with secondary acute myeloid leukaemia (AML). It should therefore not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed. However, patients should take special care before performing tasks requiring their attention, until they know how they will react to PEGYLASTIN.

INTERACTIONS

- Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, PEGYLASTIN should be administered approximately 24 hours after administration of cytotoxic chemotherapy. PEGYLASTIN can safely be administered 14 days before chemotherapy. Concomitant use of PEGYLASTIN with any chemotherapy medicine has not been evaluated in patients. In animal models, concomitant administration of PEGYLASTIN and 5-fluorouracil (5-FU) or other anti-metabolites has been shown to potentiate myelosuppression.
- Possible interactions with other haematopoietic growth factors and cytokines have not been specifically investigated.
- The potential for interaction with lithium, which also promotes the release of neutrophils, has

not been specifically investigated. There is no evidence that such an interaction would be harmful.

- The safety and efficacy of PEGYLASTIN have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression e.g. nitrosoureas.
- Specific interaction or metabolism studies have not been performed; however, clinical studies have not indicated an interaction of PEGYLASTIN with any other medicines.

HUMAN REPRODUCTION

Pregnancy:

Safety and/or efficacy during pregnancy has not been established.

There are no adequate data from the use of PEGYLASTIN in pregnant women. Animal studies have shown reproductive toxicity. The potential risk for humans is unknown.

PEGYLASTIN should not be used during pregnancy unless clearly necessary.

Lactation:

There is no clinical experience with lactating women, therefore PEGYLASTIN should not be administered to women who are breastfeeding.

DOSAGE AND DIRECTIONS FOR USE

PEGYLASTIN therapy should be initiated and supervised by healthcare providers experienced in oncology and/or haematology.

PEGYLASTIN is for single use only.

PEGYLASTIN is a sterile but unpreserved solution.

One 6 mg dose of PEGYLASTIN is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy.

There are insufficient data to recommend the use of PEGYLASTIN in children and adolescents under 18 years of age.

Before administration, PEGYLASTIN solution should be inspected for visible particles. Only a solution that is clear and colourless should be injected.

Excessive shaking may aggregate pegfilgrastim, as in PEGYLASTIN, rendering it biologically inactive.

Allow the pre-filled syringe to reach room temperature before injecting.

No dose change is recommended in patients with renal impairment, including those with end-stage renal disease.

SIDE EFFECTS:

Blood and lymphatic system disorders:

Frequent: thrombocytopenia, leucocytosis

Less frequent: sickle cell crisis, splenomegaly, splenic rupture, anaemia

Immune system disorders:

Less frequent: allergic type reactions (including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea, erythema, flushing and hypotension)

Metabolism and nutrition disorders:

Less frequent: hypokalaemia, increased uric acid levels

Nervous system disorders:

Frequent: headache

Vascular disorders:

Less frequent: epistaxis, cutaneous vasculitis, capillary leak syndrome

Respiratory, thoracic and mediastinal disorders:

Less frequent: respiratory failure, acute respiratory distress syndrome, interstitial pneumonia, pulmonary oedema, pulmonary infiltrates, pulmonary fibrosis

Gastrointestinal disorders:

Frequent: nausea

Less frequent: gastrointestinal disturbances

Musculoskeletal, connective tissue and bone disorders:

Frequent: arthralgia, myalgia, back, limb, bone, musculoskeletal and neck pain

Renal and urinary disorders:

Frequent: dysuria

Less frequent: glomerulonephritis

General disorders and administration site conditions:

Frequent: injection site pain, chest pain (non-cardiac), pain

Investigations:

Frequent: elevated alkaline phosphatase and lactate dehydrogenase.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no experience with overdose of PEGYLASTIN in humans (see SIDE EFFECTS).

IDENTIFICATION:

Clear and colourless liquid, free from visible particles.

PRESENTATION:

PEGYLASTIN presents either as a pre-filled syringe or a pre-filled injector.

Pre-filled syringe: 1 mL clear, colourless, Type I borosilicate glass, pre-filled syringe with a permanently attached stainless steel injection needle, with a needle safety guard. The needle cover of the pre-filled syringe contains dry natural rubber.

Each pre-filled syringe contains 0,6 mL of solution for injection. Pack size of one pre-filled syringe with one alcohol swab, in a blistered packaging.

Pre-filled injector: 1 mL clear, colourless, Type I borosilicate glass, pre-filled syringe with a permanently attached stainless steel injection needle. The pre-filled syringe is externally equipped with the device for self-administration (pre-filled injector). The needle cover of the pre-filled syringe contains dry natural rubber.

Each pre-filled syringe injector contains 0,6 mL of solution for injection. Pack size of one pre-filled injector with one alcohol swab, in a blistered packaging.

For single use only. One pre-filled syringe or pre-filled injector is packed in an outer carton.

STORAGE INSTRUCTIONS:

Store at 2 – 8 °C (in a refrigerator). Do not freeze.

Keep pre-filled syringe in outer carton to protect from light.

PEGYLASTIN may be exposed to room temperature (at or below 25 °C) for a maximum single period of up to 15 days.

PEGYLASTIN left at room temperature for more than 15 days should be discarded.

Do not use after the expiry date printed on the pack.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

53/8.5/0329

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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