Date: 26/1/2014

Direct Health Care Professional Communication.

Filgrastim (Neupogen®) and risk of capillary leak syndrome in patients with cancer and in healthy donors.

Pegfilgrastim (Neulasta®) and risk of capillary leak syndrome in patients with cancer

Dear Healthcare Professional,

Roche as Marketing Authorization Holder of Neupogen and Neulastim in Saudi Arabia would like to inform you that Amgen Europe B.V., (Marketing Authorization Holder of the products in the EU) has added capillary leak syndrome (CLS) as an adverse event to the product information.

Summary

• CLS has been reported in recipients of filgrastim including patients undergoing chemotherapy and a healthy donor undergoing peripheral blood progenitor cell mobilization.

• CLS has been reported in recipients of pegfilgrastim undergoing chemotherapy.

• Episodes vary in severity and frequency and may be fatal. CLS is characterized by hypotension, hypoalbuminaemia, oedema and haemoconcentration.

• Healthcare professionals should closely monitor for CLS symptoms in patients and healthy donors receiving filgrastim or pegfilgrastim.

Standard symptomatic treatment should be given immediately if symptoms occur (this may include intensive care).

• Patients and healthy donors should be advised to contact their doctor immediately if they develop symptoms (often with rapid onset) such as generalized body swelling, puffiness (which may be associated with passing water less frequently), difficulty breathing, abdominal swelling and tiredness.

• The benefits of filgrastim and pegfilgrastim continue to outweigh any risks in the approved indications.

Further information on the safety concern:

CLS has been reported in patients with cancer undergoing chemotherapy and a healthy donor undergoing peripheral blood progenitor cell mobilization who were receiving the granulocyte colony-stimulating factor (G-CSF) products filgrastim or pegfilgrastim. Reports have generally involved people with advanced malignant diseases, sepsis, those taking multiple chemotherapy medications or those undergoing aphaeresis. The mechanism of CLS remains unclear.

For filgrastim, 34 post-marketing reports of CLS were received world-wide between April 1991 and August 2012. Of these, one case concerned a healthy donor undergoing stem cell mobilization and apheresis. In 12 cases, the symptoms abated or resolved following the filgrastim's discontinuation (positive de-challenge) with supportive treatment or corticosteroids. In the majority of cases, the CLS symptoms occurred after the first dose of filgrastim treatment. In 2 cases the symptoms occurred after the first dose and re-occured after the drug was restarted (positive re-challenge) . Six cases had a fatal outcome from CLS.

For pegfilgrastim, 4 post-marketing reports of CLS were received world-wide between August 2002 and August 2012. CLS symptoms appeared after the second dose of pegfilgrastim in 2 cases. In 1 of these cases CLS occurred one day after Pegfilgrastim, suggesting a temporal association. In another case, the patient had a fatal outcome from CLS.

The total number of CLS reports expressed above has been seen in over 8.5 million patients exposed to filgrastim and over 4 million patients exposed to pegfilgrastim in the post-marketing setting.

Indications and Potential Uses of Pegfilgrastim.

To shorten the duration of neutropenia and reduce the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for a malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndrome).

Indications and potential Uses of Filgrastim.

•Established cytotoxic chemotherapy

Neupogen is indicated for reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia and its clinical sequelae in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.

•Peripheral blood progenitor cell mobilization (PBPC)

Neupogen is indicated for the mobilization of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy and the mobilization of peripheral blood progenitor cells in normal donors (allogeneic PBPC).

•Severe chronic neutropenia (SCN)

Long-term administration of Neupogen is indicated in patients, children or adults, with severe congenital, cyclic or idiopathic neutropenia with an Absolute Neutrophil Count (ANC) $\leq 0.5 \times 10^9/l$ and a history of severe or recurrent infections, to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

•HIV infection

Neupogen is indicated for the treatment of persistent neutropenia (ANC) $\leq 0.5 \times 10^9$/l in patients with advanced HIV infection, in order to reduce the risk of bacterial infections, when other options to manage neutropenia are inappropriate.

•Patients with Acute Myeloid Leukemia

Neupogen is indicated to reduce the duration of neutropenia and related clinical sequelae in patients undergoing induction or consolidation chemotherapy.

Call for reporting

Health care professionals should report any serious adverse events suspected to be associated with the use of filgrastim and pegfilgrastim according to Saudi Food and Drug Authority (SFDA) reporting requirements.
The National Pharmacovigilance & Drug safety Centre (NPC)
Saudi Food and Drug Authority (SFDA)
Fax: +966-11-2057662
Email: Npc.drug@sfda.gov.sa
Online: http://ade.sfda.gov.sa/

Company contact point

Should you have any questions or require additional information regarding the use of Filgrastim or Pegfilgrastim please feel free to contact.

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Sincerely Yours,

Hazem Al-Dajani	Naser Al-Rajhi	Tamer Elmahallawy
Local Safety Responsible	Scientific office director	Medical Director
9/2/2014	9. Feb. 2014	10. Feb. 2014