Cherubino Ltd.
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YOUR HEALTH AT HEART

Direct Health Care Professional Communication

Pegfilgrastim (Neulasta) is associated with a risk of capillary leak syndrome in patients with cancer

Dear Healthcare Professional,

Amgen Inc., in agreement with the European Medicines Agency and Medicines Authority would like to inform you about an adverse effect of capillary leak syndrome (CLS) associated with filgrastim and pegfilgrastim.

Summary

- **CLS has been reported in recipients of filgrastim including patients undergoing chemotherapy and a healthy donor undergoing peripheral blood progenitor cell mobilisation.**
- **CLS has been reported in recipients of pegfilgrastim undergoing chemotherapy.**
- **Episodes vary in severity and frequency and may be fatal. CLS is characterised 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 generalised 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 mobilisation 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 mobilisation and apheresis. In 12 cases, there was a 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 with a positive re-challenge during the second dose. 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 have been seen in over 8.5 million patients exposed to filgrastim and over 4 million patients exposed to pegfilrastim in the post-marketing setting.

The Summaries of Product Characteristics and Patient Information Leaflets for filgrastim and pegfilgrastim have been updated to reflect the new safety information [see Annexe].

Call for reporting

Healthcare professionals should report any adverse reactions suspected to be associated with the use of filgrastim or pegfilgrastim products to the Medicines Authority. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Additionally, any such information may be reported to Amgen, via Cherubino LTD pharmacovigilance@cherubino.com.mt

Company contact point

Should you have any questions or require additional information regarding the use of Neulasta, please contact Medical Information on care@cherubino.com.mt.

Sincerely,

Luisa de Piro O'Connell
RP Cherubino LTD