Amgen Receives Positive CHMP Opinion For Delivery System Of Neulasta® (pegfilgrastim)

February 27, 2018

Innovative Neulasta® Onpro® Kit is Designed to Provide the Right Dose for Patients at the Right Time

THOUSAND OAKS, Calif., Feb. 27, 2018 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion recommending a label variation for Neulasta® (pegfilgrastim) to include the Neulasta® Onpro® Kit. The Neulasta Onpro Kit combines the efficacy of Neulasta with an innovative on-body injector (OBI) delivery system. Neulasta is indicated in the European Union (EU) for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

"With more than 30 years of experience in granulocyte-colony stimulating factor (G-CSF) research, Amgen is committed to providing innovative solutions and developing new ways to improve the patient experience that also bring value to healthcare providers and health systems," said David M. Reese, M.D., senior vice president of Translational Sciences and Oncology at Amgen. "The Neulasta Onpro Kit is a showpiece of our patient-centric approach and continued investment in advancing the field of G-CSF administration. This improved administration option not only provides patients with the freedom and independence they seek, but the optimally timed delivery gives peace of mind to physicians and caregivers knowing it helps fight the risk of infection."

One of the most common side effects of myelosuppressive chemotherapy (chemotherapy that decreases the activity of the bone marrow) is a low white blood cell count, or neutropenia. Febrile neutropenia (neutropenia with fever) is a life-threatening complication of myelosuppressive chemotherapy that is associated with an increased risk of hospitalization that is costly to treat.[1]

The Neulasta Onpro Kit includes a specifically designed Neulasta pre-filled syringe along with a single use OBI. The small, lightweight OBI is applied to a patient's skin on the same day of chemotherapy. The OBI is intended to facilitate timed delivery of the correct dose of Neulasta and to improve the quality of life of patients as it removes the burden to return to a healthcare setting the day following chemotherapy, providing advantages over the standard manual injection pre-filled syringe.

Following the CHMP positive opinion, the centralized European marketing authorization of Neulasta will be updated to include the delivery system of the OBI in its label. Norway, Iceland and Liechtenstein, as members of the European Economic Area (EEA), will take corresponding decisions on the basis of the opinion of the European Commission. The Neulasta Onpro Kit has been approved in the U.S. since August 2015.

About Febrile Neutropenia

One of the most common side effects of myelosuppressive chemotherapy is a low white blood cell count. An abnormally low level of neutrophils, an important infection-fighting white blood cell, is called neutropenia. The fewer neutrophils a patient has – and the longer the neutrophil count remains low – the greater the risk of developing a potentially serious infection.[2]

Febrile neutropenia is neutropenia complicated by a fever. Fever is frequently a sign of infection and, in patients receiving myelosuppressive chemotherapy, it can sometimes be the only sign. Febrile neutropenia is a medical emergency and is associated with several potential downstream consequences.

About Neulasta® (pegfilgrastim)

Neulasta was approved for use in Europe in 2002, and is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Neulasta was also approved for use in the U.S. in 2002, and is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Neulasta is also indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation. Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

EU Important Safety Information

Special warnings and precautions for use

Traceability

In order to improve the traceability of G-CSFs, the trade name of the administered product should be clearly recorded in the patient file.

Limited clinical data suggest a comparable effect on time to recovery of severe neutropenia for pegfilgrastim to filgrastim in patients with *de novo* acute myeloid leukaemia (AML) (see section 5.1). However, the long-term effects of Neulasta have not been established in AML; therefore, it should be used with caution in this patient population.

G-CSF can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

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

The safety and efficacy of Neulasta administration in *de novo* AML patients aged < 55 years with cytogenetics (15;17) have not been established.

The safety and efficacy of Neulasta have not been investigated in patients receiving high dose chemotherapy. This medicinal product should not be

used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.

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 section 4.8).

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 Acute Respiratory Distress Syndrome (ARDS). In such circumstances Neulasta should be discontinued at the discretion of the physician and the appropriate treatment given (see section 4.8).

Glomerulonephritis
Glomerulonephritis has been reported in patients receiving NEUPOGEN (filgrastim) and Neulasta. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of NEUPOGEN and Neulasta. Urinalysis monitoring is recommended.

Capillary leak syndrome
Capillary leak syndrome has been reported after G-CSF administration and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. 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 section 4.8).

Splenomegaly and splenic rupture
Generally asymptomatic cases of splenomegaly and cases of splenic rupture, including some fatal cases, have been reported following administration of Neulasta (see section 4.8). Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.

Thrombocytopenia and anaemia
Treatment with Neulasta 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.

Medication error as a result of device failure
There is a risk of medication error, particularly a partial or missed dose of Neulasta, in the event of a device failure or malfunction with the on-body injector. In the event of a partial or missed dose, patients may be at increased risk of events such as neutropenia, febrile neutropenia and/or infection than if the dose had been correctly delivered. The healthcare professional must ensure the patient receives appropriate training about the on-body injector and understands that if they suspect a device failure or malfunction the patient must immediately inform a healthcare professional as they may need a replacement dose. Comprehensive instructions for use for healthcare professionals and patients are given in the package leaflet. The patient should also be given the Patient Alert Card.

Sickle cell anaemia
Sickle cell crises have been associated with the use of Neulasta in patients with sickle cell trait or sickle cell disease (see section 4.8). Therefore, physicians should use caution when prescribing Neulasta in patients with sickle cell trait or sickle cell disease, should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis.

Leukocytosis
White blood cell (WBC) counts of 100 x 10^9/L or greater have been observed in less than 1% of patients receiving Neulasta. No adverse events directly attributable to this degree of leukocytosis 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 this medicine. Consistent with the clinical effects and the potential for leukocytosis, a WBC count should be performed at regular intervals during therapy. If leukocyte counts exceed 50 x 10^9/L after the expected nadir, this medicine should be discontinued immediately.

Hypersensitivity
Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with Neulasta. Permanently discontinue Neulasta in patients with clinically significant hypersensitivity. Do not administer Neulasta to patients with a history of hypersensitivity to Neulasta or NEUPOGEN. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against Neulasta is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

Other warnings
The safety and efficacy of Neulasta for the mobilisation of blood progenitor cells in patients or healthy donors has not been adequately evaluated.

The needle cap of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

The on-body injector uses an acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in an allergic reaction.

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.

Neulasta contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Neulasta contains less than 1 mmol (23 mg) sodium per 6 mg dose, i.e. essentially 'sodium-free'.

Please refer to the Summary of Product Characteristics for full European prescribing information.

U.S. Important Safety Information

Contraindication
Do not administer Neulasta® to patients with a history of serious allergic reactions to pegfilgrastim or filgrastim.

Splenic Rupture
Splenic rupture, including fatal cases, can occur following the administration of Neulasta®. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Neulasta®.

Acute Respiratory Distress Syndrome
Acute respiratory distress syndrome (ARDS) can occur in patients receiving Neulasta®. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Neulasta for ARDS. Discontinue Neulasta® in patients with ARDS.

Serious Allergic Reactions
Serious allergic reactions, including anaphylaxis, can occur in patients receiving Neulasta®. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Neulasta® in patients with serious allergic reactions.

Allergies to Acrylics
The on-body injector for Neulasta® uses acrylic adhesive. For patients who have reactions to acrylic adhesives, use of this product may result in a significant reaction.

Use in Patients with Sickle Cell Disorders
Severe sickle cell crises can occur in patients with sickle cell disorders receiving Neulasta®. Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.

Glomerulonephritis
Glomerulonephritis has been reported in patients receiving Neulasta®. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after withdrawal of Neulasta®. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of Neulasta®.

Leukocytosis
White blood cell counts of 100 x 10^9/L or greater have been observed in patients receiving pegfilgrastim. Monitoring of CBCs during pegfilgrastim therapy is recommended.

Capillary Leak Syndrome
Capillary leak syndrome has been reported after granulocyte colony-stimulating factor (G-CSF) administration, including Neulasta®, and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. 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.

Potential for Tumor Growth Stimulatory Effects on Malignant Cells
The granulocyte colony-stimulating factor (G-CSF) receptor, through which pegfilgrastim and filgrastim act, has been found on tumor cell lines. The possibility that pegfilgrastim acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim is not approved, cannot be excluded.

The most common adverse reactions (≥ 5% difference in incidence) in placebo-controlled clinical trials are bone pain and pain in extremity.

Please see additional Neulasta® Safety Information, by visiting www.amgen.com/medpro/products.html.

Please see the Neulasta Full Prescribing Information by clicking here.

About Amgen's Commitment to Oncology
Amgen Oncology is committed to helping patients take on some of the toughest cancers, such as those that have been resistant to drugs, those that progress rapidly through the body and those where limited treatment options exist. Amgen's supportive care treatments help patients combat certain side effects of strong chemotherapy, and our targeted medicines and immunotherapies focus on more than a dozen different malignancies, ranging from blood cancers to solid tumors. With decades of experience providing therapies for cancer patients, Amgen continues to grow its portfolio of innovative and biosimilar oncology medicines.

About Amgen
Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com and follow us on www.twitter.com/amgen.

Forward-Looking Statements
This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins,

capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including our most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and current reports on Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for us to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints we have selected. We develop product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as we may have believed at the time of entering into such relationship. Also, we or others could identify safety, side effects or manufacturing problems with our products, including our devices, after they are on the market.

Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities, including in Puerto Rico, and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. The discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on our business and results of operations. Our efforts to acquire other companies or products and to integrate the operations of companies we have acquired may not be successful. A breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of our systems and our data. Our stock price is volatile and may be affected by a number of events. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or our ability to pay a dividend or repurchase our common stock. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all.

The scientific information discussed in this news release related to new indications for our products is preliminary and investigative and is not part of the labeling approved by the EMA for these products. These products are not approved by the EMA for the investigational use(s) discussed in this news release, and no conclusions can or should be drawn regarding the safety or effectiveness of the products for these uses.

CONTACT:
Amgen, Thousand Oaks
Kristen Davis, 805-447-3008 (Media)
Kristen Neese, 805-313-8267 (Media)
Arvind Sood, 805-447-1060 (Investors)

Amgen, Europe
Emma Gilbert, +41 413692542

References:

1.Weycker D, et al. Cost of neutropenic complications of chemotherapy. *Annals of Oncology.* 2008:19(3):454-460.
2.American Cancer Society. Low white blood cell (neutrophil) counts and the risk of infection. https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/infections/infections-in-people-with-cancer/low-wbc-and-weak-immune-system.html. Accessed Feb. 22, 2018.

of-neulasta-pegfilgrastim-300604440.html

SOURCE Amgen