Title: *Users of pegfilgrastim less than or equal to 13 years of age*

Amgen Protocol Number: 20200114

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1. BACKGROUND AND RATIONALE

On 08 November 2018, the FDA informed Amgen that they were evaluating pegfilgrastim Injection medication errors associated with doses less than 6 mg (0.6 mL) in pediatric patients weighing less than 45 kg.

The FDA requested the following information from Amgen:

1. *"An analysis of your U.S. and foreign postmarket serious and non-serious medication error/adverse event cases and complaints associated with Pegfilgrastim Injection and suspected wrong dose errors (including but not limited to overdose, underdose, dose omission, and dose confusion) involving the preparation and administration of doses less than 6 mg (0.6 mL). You should limit your analysis to cases and complaints received in the last 5 years. Your analysis should include:*
2. *Describe the trends and use of Pegfilgrastim Injection in U.S. pediatric patients weighing less than 45 kg (using ≤ 13 years of age as a surrogate for weight) in the last 3 years.*
3. *A description of your plans to prevent wrong dose errors in patients requiring Pegfilgrastim doses less than 6 mg (0.6 mL). It would be helpful if you could include discussion on any recommendations or suggestions made by a reporter such as including a dosage form suitable for pediatric doses and addition of syringe markings to measure doses less than 6 mg (0.6 mL)."*

To address the above outlined summary, the study protocol (20180440) was excuted and completed, including a CSR.

On 10 October 2019, Amgen received a Complete Response Letter and Order Letter from the FDA regarding the prior approval labeling supplement that was submitted in response to the FDA's concerns regarding pediatric dosing errors.

- The Agency concluded that the Pegfilgrastim pediatric dosing errors and their potential clinical consequences, cannot be appropriately and fully addressed through changes to Pegfilgrastim product labeling alone.
- Amgen is expected to develop a presentation that can be used to directly and accurately administer Pegfilgrastim (pegfilgrastim) to pediatric patients who weigh < 45 kg and require doses that are < 0.6 mL (6 mg).
- Amgen is required to conduct any necessary human factors studies to evaluate the ability of HCPs and/or caregivers to administer the appropriate doses.
- Amgen must submit a proposal to address the requirements set forth in the abovementioned letter within 90 days from the date of the letter.

In response, on 08 Jan 2020, Amgen submitted a response to the FDA Pediatric Assessment Required Letter which included a proposal to address FDA concerns. Amgen's proposal consisted of a presentation for pediatric administration of a

single-use, disposable, vial intended for administering a variable, weight-based dose via a .01 mL graduated syringe in pediatric patients by a caregiver in the home setting or by the healthcare provider in a clinic setting.

On 10 Feb 2020, Amgen received FDA's feedback to the response submitted on 08 January 2020:

- The FDA remains concerned that Amgen's planned approach may not be adequate to accurately administer Pegfilgrastim to pediatric patients who weigh less than 45 kg and require doses that are less than 0.6 mL (6 mg).
- The FDA recommends development of a separate lower-concentration Pegfilgrastim vial presentation with appropriate clinical studies to evaluate safety/efficacy/PK of this formulation for pediatric patients.
- The FDA acknowledged Amgen's proposal of a vial intended for administration of a variable, weight-based dose via a 0.01mL graduated syringe in pediatric patients by a caregiver in the home setting or by the healthcare provider in a clinic setting. However, the Agency is concerned that users may not be able to navigate the use of this vial and syringe in the real-world setting. The FDA recommended Amgen to submit the HF validation study protocol for feedback from the Agency before commencing the study.

To support the design of the Human factor (HF) study Amgen would like to understand the utilization frequency of Pegfilgrastim and in what setting Pegfilgrastim is being administered, among patients ages < 2 years (a surrogate for weight < 10 kg), as well as various age ranges that correspond to weight < 45kg. The results from this analysis will help inform the Regulatory and Safety team in terms of how to respond to the FDA inquiry. The results may be used in a CSR that would accompany the follow-up correspondence with the FDA.

2. OBJECTIVES

The primary objectives of this study are:

Describe the users of pegfilgrastim between 01/01/2013 and 12/31/2018 stratified by calendar year and by place-of-service for administration of pegfilgrastim, for the following age populations:

a. Patients aged ≤ 13 years;
b. (Subset) Patients aged < 2 years;
c. Patients by individual ages (< 1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 years)
d. Patients aged 0 -< 2, 2 - 5, 6 – 10, 11-13 years

3. STUDY POPULATION/SAMPLE SIZE/STATISTICAL ANALYSES PLANS

The Truven MarketScan® database[1] captures person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services from a selection of large employers, health plans, and government and public organizations. The MarketScan® databases link paid claims and encounter data to detailed patient information across sites and types of providers, and over time. The annual medical databases include private sector health data from approximately 100 payers. Our study population was extracted from both "Commercial Claims and Encounters (Commercial) Database" and the "Medicare Supplemental and Coordination of Benefits (Medicare) Database", which is what makes up the MarketScan Commercial Database. The MarketScan Commercial Database contains the inpatient, outpatient, and outpatient prescription drug experience of employees and their dependents, covered under a variety of fee-for-service and managed care health plans, including exclusive provider organizations, PPOs, POS plans, indemnity plans, and health maintenance organizations (HMOs).

Users of pegfilgrastim will be identified as patients who received their first administration of pegfilgrastim between 01 January 2013 and 31 December 2018 without any prior use of pegfilgrastim. Users of pegfilgrastim will be identified in the database as patients with at least one claim with HCPCS code ("J2505", "C9119", "S0135") or at least one claim with an NDC code ("54868522900", "55513019001", "55513019201") for pegfilgrastim. There will be no continuous enrollment required for users of pegfilgrastim. The age of users of pegfilgrastim will be defined as the difference between year of first pegfilgrastim administration and year of birth (date of birth is not available in the database).

The results will be stratified by age at first administration and reported by 12-month intervals (Table 1A-1C):

- Ages ≤ 13 years;
    - Subset population of ages < 2 years;
- By Individual Age for < 1 to 13 years;
- Age ranges: 0 - < 2, 2 - 5, 6 - 10, 11 – 13 years.

Stratify the above sets of results by Place-of-Service, in particular home vs hospital vs clinic vs other vs vs missing-data (Table 2A -2C).

To assess the number and frequency of pediatric patients that use pegfilgrastim on label as compared to off-label use, a sensitivity analysis will be conducted as follows: among

all patients identified as pegfilgrastim users, if a patient has evidence of a non-myeloid cancer diagnosis occurring any time prior to the first pegfilgrastim exposure the patient will be considered "on-label" exposed, however if no occurrence of non-myeloid cancer diagnosis is found, the patient will be categorized as "off-label". The definition of a non-myeloid cancer will be: 1 inpatient diagnostic claim or 2 outpatient diagnostic claims (at least 7 days apart) for the same non-myeloid cancer. The number and frequency of patients on label and off-label will be calculated for ages < 2 years and ages ≤ 13 years, stratified by calendar year (Table 1A-Sensitivity). Pending the available sample size, tables 1B, 1C, and possibly 2A will be replicated, stratifying by on-label and off-label results.

Table Shells

Table 1A. Number of Users of Pegfilgrastim Stratified by Age ≤ 13 and Age < 2 at First Administration

	Age < 2		Age ≤ 13 years	
12-month intervals	**n**	**%**	**n**	**%**
1 Jan 2013 - 31 Dec 2013	n	%	n	%
1 Jan 2014 - 31 Dec 2014	n	%	n	%
1 Jan 2015 - 31 Dec 2015	n	%	n	%
1 Jan 2016 - 31 Dec 2016	n	%	n	%
1 Jan 2017 - 31 Dec 2017	n	%	n	%
1 Jan 2018 – 31 Dec 2018	n	%	n	%
Total	n	%	n	%

Table 1A. Sensitivity: Number of Users of Pegfilgrastim Stratified by Age ≤ 13 and Age < 2 at First Administration

	Age < 2				Age ≤ 13 years			
Label Use	**On-Label**		**Off-Label**		**On-Label**		**Off-Label**	
12-month intervals	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
1 Jan 2013 - 31 Dec 2013	n	%	n	%	n	%	n	%
1 Jan 2014 - 31 Dec 2014	n	%	n	%	n	%	n	%
1 Jan 2015 - 31 Dec 2015	n	%	n	%	n	%	n	%
1 Jan 2016 - 31 Dec 2016	n	%	n	%	n	%	n	%
1 Jan 2017 - 31 Dec 2017	n	%	n	%	n	%	n	%
1 Jan 2018 – 31 Dec 2018	n	%	n	%	n	%	n	%
Total	n	%	n	%	n	%	n	%

Table 1B. Number of Users of Pegfilgrastim Stratified by Individual Age at First Administration

	Ages (in Years)													
	< 1	1	2	3	4	5	6	7	8	9	10	11	12	13
12-month intervals	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
1 Jan 2013 - 31 Dec 2013														
1 Jan 2014 - 31 Dec 2014														
1 Jan 2015 - 31 Dec 2015														
1 Jan 2016 - 31 Dec 2016														
1 Jan 2017 - 31 Dec 2017														
1 Jan 2018 – 31 Dec 2018														
Total														

Table 1C. Number of Users of Pegfilgrastim Stratified by Age-categories at First Administration

	Age 0 - < 2		Age 2- 5		Ages 6-10		Ages 11 - 13	
12-month intervals	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
1 Jan 2013 - 31 Dec 2013	n	%	n	**%**	n	%	n	**%**
1 Jan 2014 - 31 Dec 2014	n	%	n	**%**	n	%	n	**%**
1 Jan 2015 - 31 Dec 2015	n	%	n	**%**	n	%	n	**%**
1 Jan 2016 - 31 Dec 2016	n	%	n	**%**	n	%	n	**%**
1 Jan 2017 - 31 Dec 2017	n	%	n	**%**	n	%	n	**%**
1 Jan 2018 – 31 Dec 2018	n	%	n	**%**	n	%	n	**%**
Total	n	%	n	**%**	n	%	n	**%**

Table 2A. Place of Service for Administration of Neulasta Stratified by Age

	Age < 2					Age ≤ 13 years				
	Home	**Hospital**	**Clinic**	**Other**	**Missing**	**Home**	**Hospital**	**Clinic**	**Other**	**Missing**
12-month intervals	**N (%)**	**N (%)**	**N(%)**	**N(%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N(%)**	**N (%)**
1 Jan 13 - 31 Dec 13										
1 Jan 14 - 31 Dec 14										
1 Jan 15 - 31 Dec 15										
1 Jan 16 - 31 Dec 16										
1 Jan 17 - 31 Dec 17										
1 Jan 18 – 31 Dec 18										
Total										

The Table 2A will be regenerated for each defined age category: by individual age (Table 2b) and by age-groups 0- < 2, 2-5, 6-10, 10-13 (Table 2c).

Althoughthe Truven Marketscan database includes patients enrolled in Medicare Supplemental but, it does not include traditional Medicare enrollees. Thus, proportion of users of pegfilgrastim ≤ 13 years of age and the subset of patients < 2 years of age may be an overestimation of the national proportion of users of pegfilgrastim ≤ 13 years and < 2 years of age.

4. COLLECTION, RECORDING, AND REPORTING OF SAFETY INFORMATION AND PRODUCT COMPLAINTS

4.1 Safety Collection and Recording Requirements

This study is analyzing secondary data from Truven Marketscan commercial claims database and no safety data will be collected or reported.

5. SUBJECT CONFIDENTIALITY

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or collection of additional subject data will occur. Study results will be in tabular form and aggregate analyses that omits subject identification. Any publications and reports will not include subject identifiers.

6. PUBLICATION INTENT

The results of this study will not be published separate from submission to relevant regulatory authorities.

7. REFERENCES

1. Cappell KA, Shreay S, Cao Z, Varker HV, Paoli CJ, Gitlin M. Red blood cell (RBC) transfusion rates among US chronic dialysis patients during changes to Medicare end-stage renal disease (ESRD) reimbursement systems and erythropoiesis stimulating agent (ESA) labels. *BMC Nephrology.* 2014;15:116.