

November 5, 2018

Letter to Immune Globulin (Human) Licensed Manufacturers: Option to Lower Lot Release Specification for Required Measles Antibody Potency Testing

Under 21 CFR 640.104(b)(2), the Center for Biologics Evaluation and Research (CBER) sets the minimum specification for measles neutralizing antibody levels in Immune Globulin products. At present, the minimum level is 0.48 x CBER Standard lot 176, as adjusted to correct the difference in concentration of lot 176 (16.5%) compared with your product. As described below, in response to declining titers of measles antibodies in plasma donors, FDA is reducing the minimum measles antibody potency specification for IG products.

This letter is to inform you, a manufacturer of an IG (Human) product, that you may submit a request to lower this specification to 0.36 x CBER Standard lot 176, adjusted to correct the difference in concentration of lot 176 (16.5%) compared to that of your product. In parallel, you should add labeling to the Prescribing Information that contains corresponding recommendations for dosing of patients with Primary Humoral Immunodeficiency (PI) who have been exposed, or are likely to be exposed, to measles.

Rationale

FDA is reducing the minimum measles antibody potency specification for IG products in response to declining titers of measles antibodies in plasma donors. Declining levels of measles antibodies in plasma are caused by a decrease in the number of naturally infected donors, who have higher sustained measles antibody levels than do vaccinated donors.

Over the past several years, increasing numbers of IG product lots from different manufacturers have failed to meet the measles antibody specification. Regulation 21 CFR 211.165(f) provides that “products failing to meet established standards or specifications shall be rejected.”

If the trend of failing to meet this specification continues, we anticipate that an increasing number of IG lots will be rejected, possibly leading to product shortage. PI patients are at risk of severe measles infections if exposed to the virus. The protective serum level for immunocompetent individuals is estimated at 120 mIU/mL.¹ Although

¹ Chen RT, Markowitz LE, Albrecht P, et al. Measles antibody: reevaluation of protective titers. J Infect Dis 1990; 162: 1036-42.

the protective level for PI patients is not known, a higher level (240 mIU/mL) has been proposed by FDA.² Based on pharmacokinetic (PK) modeling, a 400 mg/kg dose of Immune Globulin Intravenous at a titer of 0.36 x CBER Standard lot 176 should provide patients with anti-measles antibody levels of at least 240 mIU/mL for up to two weeks (see Appendix).

How to Submit a Request to Lower Measles Antibody Specification to 0.36 x CBER Standard Lot 176

Form of Submission: CBE, Changes being Effected.

Content:

- Your cover letter, referencing this letter in support of your request to lower the lot release specification for measles antibodies for your product, to 0.36 x CBER Standard lot 176
- Changes to labeling, to provide information for treatment of PI patients who have been, or may be, exposed to measles, as outlined below

Labeling proposal, Section 2 in Prescribing Information for IG Intravenous (IGIV) (Human)

Under Primary Humoral Immunodeficiency:

“If a patient has been exposed to measles, it may be prudent to administer an extra dose of IGIV as soon as possible and within 6 days of exposure. A dose of 400 mg/kg should provide a serum level > 240 mIU/mL of measles antibodies for at least two weeks.”

“If a patient is at risk of future measles exposure and receives a dose of less than 530 mg/kg every 3-4 weeks, the dose should be increased to at least 530 mg/kg. This should provide a serum level of 240 mIU/mL of measles antibodies for at least 22 days after infusion.”

Labeling proposal, Section 2 in Prescribing Information for IG Subcutaneous (IGSC) (Human)

Under Primary Humoral Immunodeficiency:

“If a patient has been exposed to measles, it may be prudent to administer a dose of Immune Globulin Intravenous as soon as possible and within 6 days of exposure. A

²² FDA presentation on May 1, 2008, “FDA’s proposal to lower the minimum recommended lot release titer for measles antibodies in IGIV and IGSC,” at <https://wayback.archive-it.org/7993/20170404042943/https://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4355S1-00-index.html>

dose of 400 mg/kg should provide a serum level > 240 mIU/mL of measles antibodies for at least two weeks”.

“If a patient is at risk of future measles exposure and receives a dose of less than [insert dose] mg/kg subcutaneously per week, the dose should be increased to [insert dose] mg/kg³”.

Alternative to labeling changes for IGSC (Human)

In general, weekly or more frequent IGSC infusions result in higher IgG trough levels than monthly IGIV dosing. You may submit trough measles titer data from clinical trials, with analyses demonstrating that trough levels for your product would remain above 240 mIU/mL if the specification is lowered to 0.36 x CBER Standard lot 176.

If you have any questions, please contact the Regulatory Project Manager of this file.

Sincerely,

Wilson W. Bryan, M.D.
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Enclosure:
Appendix ‘Assumptions for PK modeling’

³ This dose may vary depending upon the IV to SC dose conversion factor recommended in the Prescribing Information for each specific product. The dose should correlate with an IV dose of 530 mg/kg every 3 weeks. The calculation should be: $530\text{mg/kg} \times [\text{product-specific factor for conversion from IGIV to IGSC}] \div 3$ [assumption that 530 mg/kg/week for 3 weeks provides serum levels of at least 240 mIU/mL].

Appendix

Assumptions for PK modeling

- The estimated titer of CBER Standard lot 176 is 42 IU/mL (16.5% solution), titrated against the 3rd international measles standard.
- Equilibration of IGIV between intravascular and extravascular compartments occurs 5 days after infusion.
- At equilibrium, 40% of IGIV is distributed intravascularly, and 60% extravascularly.
- The half-life of IGIV is estimated at 22 days.
- The estimated protective titer of measles antibodies that prevents clinical disease in healthy individuals is approximately 120 mIU/mL.⁴ The protective titer in PI patients is unknown. FDA has proposed that at least 240 mIU/mL of measles antibodies should be achieved in PI patients needing protection.

Calculation for post-infusion PK parameters, for 400 mg/kg IGIV at 0.36 x CBER Standard lot 176

Specific activity of lot 176 = 42 IU-mL/165 mg-mL = 0.25 IU/mg

0.25 IU/mg x 0.36 = 0.09 IU/mg

400 mg/kg dose x 0.09 IU/mg = 36 IU/kg dose in human

Serum titer just after infusion (C_{max}) = 36 IU/kg x kg/40 mL blood = 0.9 IU/mL, or 900 mIU/mL

Serum titer after equilibration (5 days) = 900 mIU/ml x 0.4 [40% of IG will be intravascular] = 360 mIU/mL

Serum titer at 13.5 days = **270 mIU/mL if dose is 400 mg/kg**

Serum titer at 22 days (t_{1/2}) = 360/2 = **180 mIU/mL if dose is 400 mg/kg**

Serum titer at 22 days (t_{1/2}) = **238.5 if dose is 530 mg/kg**

⁴ Chen RT, [see footnote 1.].

Caveats

- Calculations assume the worst case, that the patient has no preexisting measles titers. Most patients will have some level of measles antibodies from prior infusions.
- The true protective measles titer for PI and secondary immune-deficient patients is unknown and may differ from patient to patient.