

May 25, 2018

The Honorable Scott Gottlieb, MD  
Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Re: Petition to place arginine and lysine on the 503B bulks list or to move arginine and lysine to the 503B Category 1 list**

Dear Commissioner Gottlieb:

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) would like to provide the following inquiries and recommendations with respect to the FDA's Guidance titled "*Interim Policy on compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*".

SNMMI, composed of 17,000 members, works to set standards for molecular imaging and nuclear medicine practice by creating guidelines, sharing information through journals, hosting meetings, and leading advocacy on key issues that affect molecular imaging and therapy research and practice.

**Clinical Benefits of Lutetium Lu 177 Dotatate Therapy**

Lutetium Lu 177 dotatate therapy is a critically needed advance in patient care. The SNMMI recommends changes in the FDA guidance involving intravenous amino acid solutions administered as part of this therapy. Such changes would greatly benefit patient care and the safety of patients and hospital staff.

The FDA approved lutetium Lu 177 dotatate therapy on January 26, 2018 for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. In a phase III clinical trial, lutetium Lu 177 dotatate therapy was shown to result a 79% lower risk of disease progression or death in those treated with lutetium Lu 177 dotatate plus low dose octreotide compared to high dose octreotide.<sup>1</sup> There are few effective therapeutic options for these patients. This new therapy was added to the NCCN (National Comprehensive Cancer Network) guidelines in May of 2018 as an appropriate anticancer therapy for patients with progressive NETs.

**Amino Acid Solution**

Administration of lutetium Lu 177 dotatate can injury the kidneys. Intravenous administration of an amino acid solution is effective at reducing this renal injury and is a requirement during therapy. Per the package insert for LUTATHERA<sup>®</sup> (lutetium Lu 177 dotatate) injection,

treatment with lutetium Lu 177 dotatate requires a concomitant administration of lysine HCl and arginine HCl as a renal protectant. The specifications on the lysine HCl and arginine HCl solution are listed in the package insert (Table 1).

**Table 1. Amino Acid Solution**

| <b>Item</b>          | <b>Specification</b>  |
|----------------------|-----------------------|
| Lysine HCl content   | Between 18 g and 24 g |
| Arginine HCl content | Between 18 g and 24 g |
| Volume               | 1.5 L to 2.2 L        |
| Osmolarity           | < 1050 mOsmol         |

### **Commercial Amino Acid Solutions**

Commercially available amino acid solutions have been used as a source of the lysine and arginine in order to administer the specified amount of each. Examples of commercially available products are 10% or 15% Aminosyn™ II (Pfizer Inc., NY, NY), and 15% Clinisol (Baxter Healthcare Corporation, Deerfield, IL). Additional electrolytes are also present in many of these formulations. These commercial amino acid solutions are different than the listed indicated lysine and arginine formulation in the package insert for lutetium Lu 177 dotatate treatment and contain many other additional essential and non-essential amino acids.

These commercial amino acid solutions are not clinically preferred. They cause significant gastrointestinal distress, commonly including vomiting<sup>2, 3, 4, 5</sup>. On the other hand, patients receiving lysine and arginine solution suffered from much less vomiting incidents in comparison with patients infused with commercial solutions - 9% vs, 50%.<sup>3, 4</sup>

As a result, when using commercially available amino acid solutions during lutetium Lu 177 dotatate administration, the patient receives unnecessary amino acids and electrolytes. The significant clinical impact is that the patient experiences extreme nausea and vomiting during the lutetium Lu 177 dotatate which can persist for days. As a result, the patients suffer, may refuse future therapy and there is increased radioactive contamination resulting in increased exposure to hospital staff.

In addition to reduce side effects, lysine and arginine solution is also more effective in inhibiting renal uptake of radioactivity during peptide receptor radionuclide therapy<sup>4, 5</sup>.

### **Compounded Amino Acid Solution under 503A**

Arginine, arginine HCl, lysine, lysine HCl, are not listed in any of the three categories (i.e., Category 1, 2, or 3) of substances nominated for the 503A bulk drug substances list (bulks list). However, arginine HCl and lysine HCl are currently listed in USP 41. As such, it is possible to compound an amino acid solution containing arginine and lysine in a 503A compounding pharmacy according to a prescription specific to a particular patient following USP and state board of pharmacy guidelines.

### **Compounded Amino Acid Solution under 503B**

Nevertheless, not every facility is able to compound its own amino acid solution. Therefore, a 503B outsourcing facility would be a more suitable option as it may compound large batches with or without prescriptions to be sold to healthcare facilities. But, both arginine and lysine are listed in 503B Category 3 - Substances Nominated for the Bulks List Without Adequate Support. Hence, these two amino acids cannot be used for compounding unless they are used to compound a drug that is on the FDA's drug shortage list. This does not seem to fit in the current market situation because the commercially available amino acid solutions are less suitable for use in patients undergoing lutetium Lu 177 dotatate treatment due to the significant side effects.

### **Inquiries**

- Is/are there any particular reason(s) why arginine and lysine are included in 503B Category 3 when they are not listed in any of the 503A categories?
- Monographs currently exist for arginine HCl and lysine HCl in USP 41. Hence, should arginine and lysine remain on 503B Category 3 list?
- Since 503B Category 3 lists "arginine" and "lysine" rather than "arginine HCl" and "lysine HCl", does it mean that arginine HCl and lysine HCl (both are listed in USP 41) can be used in compounding under section 503B as long as these two amino acids are manufactured by an establishment that is registered under section 510 of the Federal Food, Drug, and Cosmetic Act and these two amino acids are accompanied by a valid certificate of analysis (COA)?

### **Recommendations**

Alternative formulations of amino acid solutions can be compounded that do not cause these severe gastrointestinal symptoms. Therefore, the SNMMI recommends the FDA support actions that result in making these alternative amino acid solutions more broadly available for clinical use in the USA.

Specifically, the SNMMI recommends the FDA consider placing arginine and lysine on the 503B bulks list so that the outsourcing facilities can start using these two amino acids in compounding the amino acid solution for lutetium Lu 177 dotatate treatment.

Alternatively, the SNMMI recommends the FDA consider moving arginine and lysine to the 503B Category 1 list – Substances Nominated for the Bulks List Currently Under Evaluation. Per the FDA policy stated in FDA's Guidance titled "*Interim Policy on compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*", the FDA does not intend to take action against an outsourcing facility for compounding a drug product from a bulk drug substance that is listed in 503B Category 1 provided that the bulk drug

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substance is manufactured by an FDA-registered establishment and is accompanied by a valid COA.

The SNMMI appreciates the opportunity to comment on FDA's Guidance titled "*Interim Policy on compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*". The SNMMI is ready to discuss any of its comments or meet with the FDA regarding the above issues. In this regard, please contact Caitlin Kubler, Associate Director, Health Policy and Regulatory Affairs, by email at [ckubler@snmmi.org](mailto:ckubler@snmmi.org) or by phone at 703-326-1190.

Sincerely,



Bennett Greenspan, MD

SNMMI President



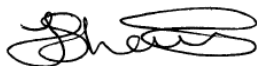
Joseph C. Hung, PhD

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## References

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- 3 Strosberg J, Krening E.  $^{177}\text{Lu}$ -dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017, 376:1391-1391 [reply].
- 4 Jamar F, Barone R, Mathieu I, et al.  $^{86}\text{Y}$ -DOTA<sup>0</sup>-D-Phe<sup>1</sup>-Tyr<sup>3</sup>-octreotide (SMT487) — a phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. *Eur J Nucl Med Mol Imaging*. 2003; 30:510-518.
- 5 Rolleman EJ, Valkema R, de Jong M, et al. Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine. *Eur J Nucl Med* 2003; 30:9-15.