

August 25, 2005

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David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products (HFD-510)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

**RE: NDA #21-839; Request that Approval be Denied**

Dear Dr. Orloff:

On August 11, 2005, Insmmed Incorporated ("Insmmed") submitted a citizen petition ("Petition") to the Food and Drug Administration ("FDA") requesting rejection of New Drug Application ("NDA") #21-839 submitted by Tercica Incorporated ("Tercica") for INCRELEX (mecasermin [rDNA origin] injection) for the long-term treatment of growth failure in children with a severe form of primary IGF-I deficiency. The Petition was assigned Docket No. 2005P-0322. On August 22, 2005, Tercica submitted comments to FDA alleging that Insmmed's Petition "is nothing more than a ploy to delay a final decision on Tercica's NDA," and is "meritless," "should not be condoned," and should be denied "for the integrity of the FDA review process." Tercica Comment at 1, 11. Insmmed considers these statements an affront to the company's integrity. The Petition, although submitted shortly before the August 31, 2005 goal date for NDA #21-839, is a sincere attempt by Insmmed to raise what the company believes are important issues related to the study of INCRELEX that not only affect the public health, but that themselves challenge the integrity of FDA's review process.<sup>1</sup>

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<sup>1</sup> As you know, on July 28, 2005, Insmmed submitted a letter to FDA's Office of Orphan Products Development ("OOPD") and to you and Dr. Dragos Roman that included arguments similar to those made in the Petition. The July 28, 2005 submission focused on Insmmed's ability to demonstrate that its SOMATOKINE (mecasermin rinfabate [rDNA origin] injection) is "clinically superior" to

Attached to this letter is a copy of a letter dated July 28, 2005 from Dr. Louis Underwood, a world renowned pediatric endocrinologist at the University of North Carolina's School of Medicine, to Dr. Marlene Haffner in OOPD. Dr. Underwood sent a copy of his letter to Tercica before the date Tercica responded to the Petition. Dr. Underwood has been intimately involved in the development of both INCRELEX and Insmed's SOMATOKINE.<sup>2</sup> In fact, Dr. Underwood was the principal investigator studying what is now Tercica's recombinant human IGF-I product. His research reportedly represents a majority of the primary data submitted in NDA #21-839.

Importantly, in his letter to OOPD, Dr. Underwood explains his concerns with respect to the quality of the clinical data supporting the safety and effectiveness of Tercica's rhIGF-I product, and notes important safety issues associated with Tercica's rhIGF-I. For example, Dr. Underwood states his expert opinion that "very high levels of free IGF-I [after the administration of rhIGF-I] are responsible for the imbalance of growth in [children with Growth Hormone Sensitivity Syndrome], i.e., overgrowth of lymphoid tissues and thickening of soft tissues of the face." Underwood Letter at 4. Tercica's comments to the Petition on this topic completely ignore the company's own investigator's concerns. Instead, Tercica resorts to labeling the "free rhIGF-I" issue raised by Insmed as a "self-interested complaint." See Tercica Comment at 6-7. Nevertheless, the fact remains that there are, at least in one expert's opinion (who is also the principal investigator for Tercica's chief clinical study), important and unresolved issues concerning Tercica's INCRELEX.

Insmed does not plan to submit Dr. Underwood's letter to Docket No. 2005P-0322, unless specifically requested to do so by FDA.<sup>3</sup> Instead, with this letter Insmed seeks to ensure FDA of the company's sincere and well-founded reasons for submitting the Petition.

Please contact me (804.565.3010) or Insmed's counsel, Frank Sasinowski at Hyman, Phelps & McNamara, P.C., (202.737.4287) if you have any questions concerning this submission.

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INCRELEX.

<sup>2</sup> The tradename SOMATOKINE was recently replaced with the tradename iPLEX. The NDA for iPLEX has been assigned #21-884. FDA action on NDA #21-884 is due by October 3, 2005.

<sup>3</sup> Certainly, Insmed does not want to be accused by Tercica of further abusing the citizen petition process and challenging the integrity of the FDA review process.

Respectfully Submitted,

A handwritten signature in black ink, appearing to read "Geoffrey Allan". The signature is fluid and cursive, with a large initial "G" and "A".

Geoffrey Allan, Ph.D.

President & Chief Executive Officer

cc: Kim E. Dettelbach, Esq.  
Elizabeth H. Dickinson, Esq.  
Marlene Haffner, M.D., M.P.H.  
John McCormick, M.D.  
Dragos Roman, M.D.  
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