



February 14, 2002

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20857

3570 '02 FEB 15 PM 2:40

Re: Docket 01P-0574/CP1

To whom it may concern:

Novartis Pharmaceuticals Corporation ("Novartis"), makes this submission in connection with the December 14, 2001 citizen petition filed on behalf of Ben Venue Laboratories, Inc. ("Ben Venue"). In that petition, Ben Venue seeks to obtain a determination that "discontinued labeling for Octreotide Acetate Injection was not withdrawn for safety or effectiveness reasons" and, additionally, that use of that labeling by a generic product would not render that product less safe or effective than the only marketed immediate-release octreotide acetate product, Sandostatin® (octreotide acetate) Injection. Novartis is making this submission to ensure that the record provides sufficient data to support a careful evaluation of this matter.

Novartis (then Sandoz Pharmaceuticals Corporation) pioneered development of octreotide acetate products for treatment of acromegaly and the symptoms of vasoactive intestinal peptide tumors (VIPomas) and carcinoid tumors. Sandostatin® (octreotide acetate) Injection was first approved by FDA in 1988 for the carcinoid and VIPoma indications; this was followed by approval for use in acromegaly in 1994 (NDA 19,667).

Shortly after it began marketing this product, Novartis undertook to re-formulate Sandostatin® Injection in response to patient reports of pain at the site of injection. Novartis determined that this pain could be reduced or eliminated when the original buffer system which contained acetic acid (and which Ben Venue seeks to reinstate) was replaced by a lactic acid buffer system. Supplemental New Drug Applications ("NDAs") for the reformulated product were approved in 1996 (for ampules) and 1994 (for multidose vials). As set forth in Novartis' cover letter to the FDA when those supplemental NDAs were filed, the company initiated the formulation change precisely because of this safety issue, i.e., "reports of pain at the site of injection."

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Efficacy is also affected by replacement of the acetic acid/sodium hydroxide buffer: to minimize the potential for injection site pain is to reduce the risk of patient non-compliance and diminished efficacy. Novartis continues to believe that only the most safe and efficacious formulation of octreotide acetate should be available for patients whose life-long struggle with carcinoid syndrome, VIPomas, or acromegaly might require them to self-administer subcutaneous injections up to three times daily.

Novartis submits for the record the report of the clinical study upon which FDA's approval of the improved re-formulation was based. Results of that study confirmed that the lactic acid-containing formulation was safer for patients than the product originally approved by FDA that contained acetic acid.¹ Accordingly, enclosed as Appendix 1 is a copy of the cover letter of the supplemental NDA in which the improved formulation was filed, as well as a copy of the report of the study supporting the change entitled, "Bioequivalence Study of the Two Parenteral Preparations of SMS 201-995."

In addition, enclosed as Appendix 2 is information from Novartis' Pharmaceutical Expert Reports for the 100 mcg/mL and 500 mcg/mL ampules. This report attributes the decrease in injection site pain, seen when acetic acid is eliminated from the formulation, to the more rapid post-injection re-establishment of physiological pH at the site of injection when the lactic acid buffer is used than when acetic acid is present in the formulation.² This is the same safety reason Novartis cited in its supplemental NDA cover letter requesting approval of the currently marketed formulation.

Appendix 3 contains several publications demonstrating consistent recognition of injection site pain across clinical trials³ with the original acetic acid formulation.

Finally, Novartis also wishes to correct a misstatement on page 3 of Ben Venue's citizen petition. Sandostatin® Injection is *never* diluted when given subcutaneously according to the approved labeling -- particularly when self-administered for acromegaly, carcinoid syndrome, or VIPomas. Therefore, Ben Venue is incorrect in asserting in their petition (page 3, paragraph 4) that "(b)oth the discontinued labeling

¹ For the original acetic acid formulation, injection site pain was reported by 9 of the 16 subjects and resolved in 10-40 minutes after injection. The currently marketed lactic acid formulation elicited only 1 report of pain, which resolved in 10 minutes, from this same group. Enclosed at Appendix 1 are copies of the submission cover letter and the report of the study entitled, "Bioequivalence Study of the Two Parenteral Preparations of SMS 201-995".

² Enclosed at Appendix 2 is an excerpt from the document, "Sandostatin® Ampoules 0.1mg/1ml (Lactic Acid/Mannitol Formulation), Part 1 C: Expert Report on 1. Chemical and Pharmaceutical Documentation", Sandoz Ltd., Basle, Switzerland, 36/40Dr. DS, June 14, 1989. A substantially identical volume was prepared in connection with the 0.5mg/mL product.

³ In one of these (Friess et al. at page 1271), among patients reporting an event (59/247), there was a 71% (25/35) incidence of injection site pain upon administration of placebo and a 75% (18/24) incidence in octreotide patients; this points even more directly at the (now-replaced) excipients as the source of this adverse reaction.

and the current labeling require dilution in 0.9% sodium chloride or in dextrose prior to administration.”

To assist practitioners in situations where the drug is administered intravenously, the labeling does provide the following information:

“Sandostatin® (octreotide acetate) is stable in sterile isotonic saline solutions or sterile solutions of dextrose 5% in water for 24 hours.”

However, it should be noted that undiluted, subcutaneous injection is the usual route of administration for treatment and/or control of symptoms of Sandostatin® Injection indications.

Novartis hopes that the data specified above and appended to this response will clarify the issues surrounding the formulation improvement that supported the development and approval of the current Sandostatin® (octreotide acetate) Injection product. Please feel free to contact the undersigned, on (973) 781-8697, if there are any questions or if additional information is required.

Respectfully submitted,



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Associate Director
Drug Regulatory Affairs

cc: Gary Buehler – HFD 600
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