CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019667/S004

Trade Name: SANDOSTATIN

Generic Name: OCTREOTIDE ACETATE

Sponsor: SANDOZ PHARMACEUTICALS

Approval Date: 06/12/91

Indication(s): TREATMENT OF ANTISECRETORY, GASTRIC (SYMPTOMATIC CONTROL IN METASTATIC CARCINOID AND VASOACTI VE INTESTINAL PEPTIDE SECRETING TUMORS)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 019667/S004

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling				X
Medical Review(s)				X
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 019667/S004

APPROVAL LETTER

NDA 19-667/S-004

JUN 12 1991

Sandoz Pharmaceuticals
Attention: Andrew N. Gustafson, Ph.D.
Route 10
East Hanover, NJ 07936

Dear Dr. Gustafson:

Reference is made to your supplemental new drug application dated December 20, 1989, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sandostatin (octreotide acetate).

The supplement provides for the addition of 200 and 1000 mcg/mL 5 mL multidose vials of Sandostatin.

We also acknowledge receipt of your amendment dated August 6, 1990, providing additional information in regard to your study entitled "Study No. 24: Bioavailability of Subcutaneous Doses of Two Strengths of Sandostatin Multiple Dose Vials Relative to the Marketed Single Dose Ampul in Healthy Male Volunteers".

We further refer to the telephone conversation on June 7, 1991 between yourself and Ms. Lana Braithwaite of this Division in which you agreed to implement the two labelling revisions in the package insert that are cited below.

We have completed our review of this supplemental application, along with the draft labelling (package insert, vial labels and carton labels), and it is approved, effective the date of this letter, with the agreed upon revisions in the package insert.

The package insert revisions are as follows:

1. In the **CLINICAL PHARMACOLOGY** section, the sentence that currently reads "In an elderly population, a slight increase in half-life and about a 25% decrease in clearance was observed." should be revised to read as follows:

   "In an elderly population, dose adjustments may be necessary due to a significant increase in the half-life (46%) and a significant decrease in the clearance (26%) of the drug."

2. To maintain consistency throughout the package insert, the amount of octreotide acetate in the single dose ampuls should be expressed in mcg.

Please submit twelve (12) copies of the final printed labeling (FPL) including the labelling revisions indicated above to FDA as soon as possible. Seven of the copies should be individually mounted on heavy weight paper or similar material. The submission should be designated for administrative purposes as "FPL for Approved NDA 19-667/S-004." Approval of the submission by FDA is not required before the labelling is used. Marketing the product with final printed labels and cartons that are not identical to the drafts submitted, and a final printed package insert that is not in accordance with the agreed upon revisions may render the product misbranded and an unapproved new drug.

In addition, we note that the autoclaving process performed on the single dose ampuls is no longer included in the manufacturing process for the multi-dose vials. Please provide a justification for this change. This information can be provided in an annual report.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Should you have any questions in regard to this letter, please contact Ms. Lana Braithwaite at (301) 443-3510.

6/11/91

Sincerely yours,

6/11/91

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: NDA Arch.
HFD-510
HFD-80
HFC-130/JAllen
HFD-420/CBradley/JHunt
HFD-500/LRipper
HFD-638
HFD-735
HFD-510/JTemeck/GTroendle/YYChiu
HFD-511/LBraithwaite/06.06.91/FT/CJC/06/11/91/N19667AP.S004
Concurrence: JShort/JTemeck/6/9/Troendle/6/10/YChiu/6/11//91

SUPPLEMENT APPROVAL/INFORMATION REQUEST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019667/S004

CHEMISTRY REVIEW(S)

ORIGINAL

APR 5 1991

CHEMIST'S REVIEW	1. ORGANIZATION DMEDP, HFD-510	2. NDA NUMBER 19-667
3. NAME AND ADDRESS OF APPLICANT Sandoz Pharmaceutical Corp. Route 10, Hanover, NJ 07936		4. SUPPLEMENT NUMBER, DATE S004, 12-20-90
6. NAME OF THE DRUG Sandostatin Injection	7. NONPROPERIETARY NAME octreotide acetate injection	9. AMENDMENTS/ REPORTS, DATE.
8. SUPPLEMENT PROVIDES FOR: two additional strengths, 200 and 1000 mcg/mL in 5 mL multidose vials.		
10. PHARMACOLOGICAL CATEGORY somatostain analogy	11. HOW DISPENSED Px	12. RELATED
13. DOSAGE FORM solution for injection (one ml)	14. POTENCY 50, 100, 500 mcg/ml	

15. CHEMICAL NAME AND STRUCTURE

D-Phe-Cys-D-Try-Lys-Thr-Cys-Thr-OH acetate

16. COMMENTS

The original supplement was not approved due to the lack of EEP clearance and the absence of validation data of the process in of the contract manufacturer. The EEP clearance was later received on 3-21-90.

was amended on 2-12-91 to include a complete validation package on the Satisfactory results are given.

17. CONCLUSION AND RECOMMENDATIONS

The information provided to their is satisfactory. This supplement is now approvable. However, the question raised in Chem. Rev dated May 18, 1990 still needs to be answer by Sandoz. In addition, for consistency, the amount of octreotide in the single dose ampuls should be expressed in mcg throughout the package insert.

18. NAME	REVIEWER SIGNATURE	DATE COMPLETED
Yuan-yuan Chiu, Ph.D.	/S/	4-5-91

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N19017.WPS

BEST POSSIBLE COPY

ORIGINAL

MAY 18 1990

CHEMIST'S REVIEW	1. ORGANIZATION DMEDP, HFD-510	2. NDA NUMBER 19-667
3. NAME AND ADDRESS OF APPLICANT Sandoz Pharmaceutical Corp. Route 10, Hanover, NJ 07936		4. SUPPLEMENT NUMBER, DATE S004, 12-20-90
6. NAME OF THE DRUG Sandostatin Injection	7. NONPROPERIETARY NAME octreotide acetate injection	9. AMENDMENTS/ REPORTS, DATE
8. SUPPLEMENT PROVIDES FOR: two additional strengths, 200 and 1000 mcg/mL in 5 mL multidose vials.		
10. PHARMACOLOGICAL CATEGORY somatostain analogy	11. HOW DISPENSED Px	12. RELATED IND/NDA/DMF
13. DOSAGE FORM solution for injection (one ml)	14. POTENCY 50, 100, 500 mcg/ml	

15. CHEMICAL NAME AND STRUCTURE

D-Phe-Cys-D-Try-Lys-Thr-Cys-Thr-OH acetate

16. COMMENTS

17. CONCLUSION AND RECOMMENDATIONS

This supplement is not approvable because (1) cGMP clearance for the contract manufacturer has not been received and (2) the DMF submitted by the contract manufacturer does not contain adequate information.

18. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Yuan-yuan Chiu, Ph.D.	/S/	5-18-90

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N19667.WPS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019667/S004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

4,1 ORIGINAL

APR 29 1991

Octreotide Acetate
SANDOSTATIN SC Injection
NDA 19-667
Reviewer: Charles R. Bradley

Addendum to a Review

In a conversation with Ms. Lana Braithwaite (CSO from HFD-510), it was learned that it was the opinion of the reviewing medical officer that the slight increase in rate of absorption for the 1.0 mg/mL multiple-dose vial for Sandostatin with respect to the approved 0.5 mg/mL single-dose vial (see Bio review dated 3/8/91) is not clinically significant. Therefore, the proposed labeling changes submitted by the sponsor in a earlier submission (see Bio review dated 3/22/90) are acceptable for this product also.

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/S/

Charles R. Bradley, Ph.D.
Pharmacokinetics Evaluation Branch

RD/FT initialed by John P. Hunt /S/ 4/29/91

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OCTREOTIDE
SANDOSTATIN^R S.C. Inj.
NDA 19-667
Reviewer: Ziad Hussein, Ph.D.
1-O, 2-P, 1-S
PC

Sandoz Pharmaceutical Corp.
Route 10, East Hanover
NJ 07936
Submission Date:
February 21, 1989

MAY 22 1990

REVIEW OF RESPONSES TO DEFICIENCIES, PROTOCOLS AND A PHARMACOKINETIC STUDY

I. BACKGROUND: Sandostatin^R (octreotide or SMS 201-995) Injection, a cyclic octapeptide analogue of somatostatine, is a sterile solution of octreotide acetate in buffered sodium chloride for administration by deep subcutaneous (intrafat) injection. Octreotide is a long-acting selective inhibitor of growth hormone indicated for the treatment of GI neuroendocrine tumors. This NDA was classified as 1A and this drug was the only drug available for certain tumor indications.

The original NDA was filed on February 6, 1987 and reviewed by the Division of Biopharmaceutics on November 6, 1987. From the biopharmaceutics point of view, the bio-studies filed under NDA 19-667 on February 6, 1987 were found to be unacceptable due to deficiencies in:

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i) the used to analyze plasma levels of octreotide

ii) the bioavailability study of subcutaneous doses of 50 mcg and 200 mcg

iii) the dose proportionality study and

iv) the pharmacokinetics of octreotide in renally impaired patients.

Despite that, because the drug was classified as 1A and there is no other alternative drug for the therapeutic indication of this drug, an approval letter dated October 21, 1988 for Sandostatin^R, signed by Dr. J. Bilstad (Director, ODE II), was forwarded to the sponsor. In the approval letter, the sponsor was requested to respond, within 120 days, to the biopharmaceutic issues raised in the bio-review dated November 6, 1988.

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The current submission includes:

i) the sponsor's responses to two of the biopharmaceutic issues

ii) protocols for two proposed BA/PK studies as response to the other two

biopharmaceutic issues raised in the bio-review and

iii) a report of a recent study.

The biopharmaceutic issues and the sponsor's responses are attached to this review

II. RESPONSE TO DEFICIENCIES

Response to Deficiency #1: The sponsor submitted four reports to support their indication that the used to assay octreotide lacks specificity when applied to bile samples but specific, particularly with rabbit antiserum, for SMS 201-995 when applied to plasma and urine. The first report compares mean plasma levels of octreotide measured by) to those in pooled plasma (5 to 6 rats or 3 dogs) measured by an method and compares the mean urinary excretion (3 rats) of unchanged octreotide measured to the urinary excretion in pooled urine (5 rats) measured The comparison of the two analytical methods showed similarity in the urinary excretion but not the plasma levels of octreotide.

The second report showed a good linear relationship (slope = 1.059) between plasma levels of octreotide measured and by a validated . The fourth report supplies results on the binding of several peptide derivatives and metabolite 1 of octreotide that indicated lack of cross-activity between the derivatives and metabolite 1 and octreotide
The sponsor submitted an Annex to Documents 303-012 and 303-016 with regard to method validation data for two pivotal studies.

Conclusion: Based upon the submitted data on February 21, 1989, the used to analyze plasma and urinary levels of octreotide seems to be specific and validated. Therefore, **the response to Deficiency #1 is acceptable.**

* * * *

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Response to Deficiency #2: In the bio-review dated November 6, 1987 of the original submission of NDA 19-667, the Division of Biopharmaceutics requested that the average absolute bioavailability of octreotide following 50 mcg and 200 mcg SC doses, that was found to be 135% (Document 303-212), needed to be conceptually explained.

In response, the firm re-analyzed the data for doses 50, 100 and 200 mcg with different statistical approaches. The absolute bioavailability of the SC administration of octreotide, calculated from the individual ratios, was found to be 110 $\pm$ 24% (median 109%) with a 95% confidence interval from 97% to 122% with respect to the IV dose.

Median of 109% was calculated with 95% confidence interval from 98% to 119%. Based on the reanalysis of the data, a bioequivalency of IV and SC doses was concluded and the labelling was changed adequately

Conclusion: The response to Deficiency #2 is acceptable.

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Response to Deficiency #3: The sponsor indicated that the pharmacokinetics of SMS 201-995 will be investigated up to 1500 mcg/day. A protocol for such a study was submitted and is evaluated under this bio-review.

Response to Deficiency #4: The sponsor indicated that the pharmacokinetics of Sandostatin in patients with different degrees of renal impairment will be investigated. A protocol for such a study was submitted and is evaluated under bio-review.

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III. PROTOCOL FOR STUDY CODE: SMS 0067

Short Title: Dose Proportionality of SMS 201-995

Objectives:

1. To evaluate the tolerability of SMS 210-995 in doses of 100 μg, 200 μg and 500 μg given subcutaneously (SC) t.i.d., in 8-hourly intervals, over a period of 7 days.

2. To assemble and compare the pharmacokinetic profiles of three different doses of SMS 201-995 after single dose administration and at the end of the multiple dose administration.

Subjects: Eighteen (18) healthy male subjects. Age: Weight: . Inclusion/exclusion criteria were adequately described.

Dosage Forms:

1.	Ampoules containing 0.1 mg octreotide/ml	NO. 71275/01, LOT NO. Y 062 0788).
2.	Ampoules containing 0.2 mg octreotide/ml	NO. 72375.01, LOT NO. Y 149 0687).
3.	Ampoules containing 0.5 mg octreotide/ml	NO> 71135.01, LOT NO. Y 185 0788).

Study Design, Dosage and Administration: This will be a double-blind, randomized, cross-over study. Each subject will receive 100 μg t.i.d., 200 μg t.i.d. and 500 μg t.i.d, as subcutaneous injections into the thigh for 5 consecutive days. On days 1 and 7 of the study periods, the subjects will receive only one dose in the morning. A washout period of 1-2 weeks will elapse between each treatment.

Blood Collection: Samples (3 ml each) will be collected at:
Days 1 and 7: At -1, 5, 10, 15, 20 min and 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20 and 24 hr post-dosing on days 1 and 7 and also at 28, 32 and 36 hours post-dosing on day 7.

Days 3, 4, 5 and 6: One sample each day immediately before the morning administration.

Analytical Methodology:

Pharmacokinetic and Statistical Analysis: Pharmacokinetic profiles of SMS 201-995 will be evaluated after single doses on days 1 and 7. The parameters assessed will be tested for normality and homogeneity. If the data fulfill these requirements the t-test will be used to test for differences in the means of the groups. If the requirements are not fulfilled, the test of Wilcixon, Mann and Whitney will be applied. Differences between the parameters of the different populations will be regarded as significant when the calculated probability of the test-statistics is below or equal to 0.05.

Comments: **(To be communicated to the sponsor)**

1. The sponsor should provide in the study's report assay validation (i.e., specificity, sensitivity, standard curves, accuracy and inter and intra-day precision data) for the that will be used to measure plasma levels of SMS 201-995 to be obtained from the proposed study.

2. The general statistical analysis approaches proposed by the sponsor to analyze the pharmacokinetic data that will be obtained from the proposed study may be employed by the sponsor as seen appropriate, but the following specific pharmacokinetic/statistical analyses should also be provided:

   i) Analysis of C_{min} values within a dosing regimen to assess when steady-state is achieved per regimen. If steady-state is achieved by Day 6, then an analysis of dose normalized $C_{min,ss}$ values on Day 6 and 7 (at 0 and 8 hours post-dosing on Day 7) using ANOVA and the Two One-Sided Tests Procedure for pairwise dosing regimen comparisons.

   ii) Ratio analyses of C_{max}, AUC_{0-8} on Day 7, and $AUC_{0-\infty}$ on Day 1 for between dose treatment comparisons of non-dose normalized C_{max} values for Day 1 and for Day 7 (i.e., per subject dose comparisons of 100 μg/0.1 ml, 200 μg/0.1 ml and 500 μg/0.2 ml).

   iii) Ratio analyses of C_{max}, AUC_{0-8}, and AUC_{0-8} on Day 7 versus C_{max}, $AUC_{0-\infty}$, and AUC_{0-8}, respectively, on Day 1 per dose level per subject.

   iv) Separate analyses of dose normalized C_{max} values for Days 1 and 7, dose normalized $AUC_{0-\infty}$ for Day 1, and for dose normalized AUC_{0-8} for Day 7 using ANOVA and the Two One-Sided Tests Procedure for pairwise dose treatment comparisons. Also, separate analyses per dose level of non-dose normalized $AUC_{0-\infty}$ for Day 1 versus non-dose normalized AUC_{0-8} for Day 7 using ANOVA and the Two One-Sided Tests Procedure for Day 1 versus Day 7 comparisons.

   v) Separate analyses of t_{max}, $t_{1/2}$, and estimated "apparent" total body clearance (CL/F) for Days 1 and 7 using ANOVA and the Two One-Sided Tests Procedure for pairwise dose comparisons. Also, separate analyses of $t_{1/2}$ and CL/F on Day 1 versus Day 7 per dose level using ANOVA and the Two One-Sided Tests Procedure.

Recommendation: The protocol for the proposed study coded SMS 0067 is acceptable provided Comments Nos. 1 and 2 are incorporated.

This Recommendation and Comments 1-3 should be forwarded to the sponsor.

IV. PROTOCOL FOR STUDY CODE: SMS 0061

Title: Pharmacokinetics of Sandostatin^R in Patients with Impaired Renal Function After a Single Subcutaneous Administration of 100 μg.

Objectives:

1. To evaluate the tolerability of SMS 201-995, given subcutaneously (SC) in a single dose of 100 μg, in patients with impaired renal function.

2. To compare the pharmacokinetic profile of SMS 201-995, given SC at a single dose of 100 mcg, between healthy subjects and patients with impaired renal function.

3. To study the protein binding of SMS 201-995 in patients with impaired renal function.

Subjects: 24 adult males or females. Age: Weight:

1. Eight (8) patients with creatinine clearance of 40-60 ml/min.
2. Eight (8) patients with creatinine clearance of 10-40 ml/min.
3. Eight (8) patients requiring hemodialysis.

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Inclusion/Exclusion criteria were adequately described.

Dosage Form: Ampoules containing 0.1 mg of SMS 210-995/0.1 ml for SC injections (No. 71275; Lot No. Y 062 0788).

Study Design and Dosage: This will be an open study where each patient will receive a single SC dose of 100 μg of SMS 201-995.

Blood and Urine Collection:

Blood: Samples will be collected at -1 hour and at 0, 5, 10, 15, 20 minutes and 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10 and 12 hours post-dosing.

Urine: One sampling pre-dosing and at intervals of 0-24 and 24-48 hours post-dosing.

Analytical Methodology:

Pharmacokinetic and Statistical Analysis: AUC, t_{max} and C_{max} values will be obtained for each patient by conventional methods. From the SMS 201-995 plasma concentration-time data of each patient the parameters of an appropriate pharmacokinetic model will be calculated with non-linear regression methods.

The results from the study will be statistically analyzed by comparing the pharmacokinetic parameters of SMS 201-995 in patients with those obtained in healthy volunteers who have received also a single SC dose of 100 mcg of SMS 201-995.

Comments: (To be Communicated to the sponsor)

1. The sponsor should provide in the study's report assay validation (i.e., specificity, sensitivity, standard curves, accuracy and inter and inter-day precision data) for the techniques that will be used to analyze plasma and urine concentrations of SMS 201-995, respectively, from the proposed study.

2. In addition to AUC, t_{max}, and C_{max}, being determined $t_{1/2}$, estimated "apparent" total body clearance (CL/F) as well as "apparent" renal clearance should be determined.

3. The elimination half-life of SMS 201-995 was in the range of 1.5-3 hours in subjects with normal renal and hepatic function. To better identify any possible prolongation in the elimination half-life of SMS 201-995 in patient with different degrees of renal insufficiency it is recommended that additional blood samples to be collected at least at 16 and 24 hours, plus possibly at 36, and 48 hours post-dosing SMS 201-995.

4. Also, to better characterize the renal clearance of SMS 201-995 in patients with impaired renal function, urine samples should be collected from 0-6, 6-12, 12-24, 24-36, and 36-48 hours post-dosing SMS 201-995, and not as proposed by the sponsor, in order to correspond with blood collections as appropriate.

5. The sponsor should define in the study's report whether the pharmacokinetics of SMS 201-995 in patients requiring hemodialysis were studied pre-, during- or post-dialysis.

Recommendation: The protocol for the proposed study coded SMS 0061 is acceptable provided Comments No. 1-5 are incorporated.

This Recommendation with Comments Nos. 1-5 should be forwarded to the sponsor.

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V. Study Code: SMS 4001

Title: Sandostatin-Tolerability and Pharmacokinetic with SMS 201-995 After S.C. Administration of a Single Dose (0.1 mg) in Elderly Volunteers.

Objective:

1. To evaluate the tolerability of SMS 201-995 given subcutaneously, as a single dose of 100 mcg, to the elderly population.

2. To study the pharmacokinetics of SMS 201-995 in the elderly, after SC injection of 100 mcg, and to compare it with that in healthy adult subjects.

Subjects: Twelve (12) elderly subjects (4 males and 8 females). Age: 68-88 years. Weight: 51-85 kg. The diagnosis of the subjects participated in the study and their concomitant therapy are listed in Table 1 (Attachment III). Exclusion criteria were adequately described.

Dosage Form: Ampoules containing 0.1 mg of SMS 210-995/0.1 ml for SC injections (No. 71275.01; lot No. Y 122 G3).

Study Design and Dosage: An open study where each subject received a single SC administration of 100 mcg SMS 201-995.

Blood Collection: Samples (2 ml) were collected at -1 (10 ml), 5, 10 and 15 minutes and 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 2.5, 4, 5, 6, 7, 8 and 10 hours post-dosing. After centrifugation at 4^0C, the plasma was transferred and deep frozen at -20^oC until analysis.

Analytical Methodology:

Pharmacokinetic and Statistical Analysis: Pharmacokinetic evaluation of the data was done for each subject. The data were analyzed with non-linear regression method by fitting the one-compartment open model to the data. C_{max} and t_{max} values were an observed values. $AUC_{0\text{-}480\ min}$ and $AUC_{0\text{-}600}$ were calculated from the data using the trapezoidal rule. The following parameters were obtained from the fitting: relative clearance (CL/F), relative volume of distribution (V/F), absorption and elimination of half-lives ($t_{1/2,abs}$ and $t_{1/2,elim}$) and $AUC_{0\text{-}infinity}$. The pharmacokinetic parameters were compared with those found after S.C. injection to 100 mcg in healthy adult subjects (study in the original submission) using the t-test and the test of Wilcixon, Mann and Whitney. The level of significance was set at $p < 0.05$.

Results: The individual and mean plasma levels in the elderly, the individual and mean pharmacokinetic parameters of SMS 201-995 in the elderly and adults and the mean

plasma profiles of SMS 201-995 in the elderly and adults are listed/illustrated in Attachment III. Shown below are the mean pharmacokinetic parameters of SMS 201-995 in the elderly and adults obtained after S.C. administration of 100 mcg of SMS 201-995:

Parameter	Elderly n=12	Adults n=16	Significancy
C_{max} (ng/ml)	4.49 ± 1.23	4.87 ± 1.60	p>0.05, N.S.
t_{max} (min)	23 ± 19	23 ± 7	p>0.05, N.S.
AUC_{0-580} (ng.min/ml)	805 ± 164 ↑24%	651 ± 162	p<0.05, S (25% ↑)
AUC_{0-inf} (ng.min/ml)	888 ± 196 ↑31%	676 ± 159	p<0.01, S (31% ↑)
t_{abs} (min)	3.37 ± 2.36	5.06 ± 3.21	p>0.05, N.S.
$t_{1/2,elim}$ (min)	140 ± 16 ↑46%	96 ± 19	p<0.01, S (46% ↑)
V/F (liter)	23.5 ± 4.0	22.0 ± 8.2	p>0.05, N.S.
CL/F (ml/min)	117 ± 24 ↓26%	159 ± 52	p<0.01, S (26% ↓)

S: Significant; NS: Not Significant.

Conclusion: The results of the statistical analysis showed that $AUC_{0-480\ min}$, $AUC_{0-infinity}$ and the elimination half-life ($t_{1/2}$) were significantly higher and the relative clearance (CL/F) was significantly lower in the elderly than in healthy adults. This could result in higher plasma levels of SMS 201-995 in the elderly than in adults after repeated treatment. Therefore, dose adjustment of SMS 201-995 might be necessary in the elderly population.

Comment: Although there were significant differences between the two populations (adults and elderly) in the AUC, relative clearance (CL/F) and elimination half-life of SMS 201-995, the sponsor concluded that "*no dose corrections are necessary if elderly patients require a treatment of SMS 201-995*". The Medical Officer (HFD-510) is recommended to consider the significant findings from this study and whether dose adjustment of SMS 201-995 might be necessary in the elderly population.

Recommendation: The pharmacokinetic study of SMS 201-995 in the elderly is acceptable. However, the Medical Officer (HFD-510) is recommended to consider whether a dose adjustment is necessary in this population as stated in the Comment section.

Overall Recommendation: The Division of Biopharmaceutics has reviewed the information/data that was filed on February 21, 1989 under NDA 19-667. The four biopharmaceutic issues that were raised in the bio-review of the original NDA submission dated February 6, 1987 were forwarded to the firm through an approval letter dated October 21, 1988 for Sandostatin^{R}. The sponsor's responses to issues 1 and 2, regarding the assay specificity and validation and the absolute bioavailability after S.C. administration, are acceptable.

In response to the other two biopharmaceutic issues regarding the pharmacokinetics of SMS 201-995 in patients with impaired renal function and the dose proportionality study, sponsor's submitted protocols for the two proposed studies appear to be acceptable provided Comments Nos. 1 and 2 for Protocol # SMS 0067 (review page 5) and Comments Nos. 1, 2, 3, 4, and 5 for Protocol # SMS 0061 (review page 7) are incorporated.

From the biopharmaceutic point of view the pharmacokinetic study of SMS 201-995 in the elderly is acceptable. [Note: **the Medical Officer (HFD-510) is recommended to consider whether a dose adjustment is necessary in this population. See the Comment and Conclusion's sections on review page 9**]

This Overall Recommendation and the different Protocols' Comments should be communicated to the sponsor.

/S/ 5/22/90

APPEARS THIS WAY
ON ORIGINAL

Ziad Hussein, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed by John P. Hunt JPH 5/10/90
FT Initialed by John P. Hunt /S/ 5/22/90

cc: NDA 19-667 Orig., HFD-510, HFD-426 (Hussein), HFD-344 (Turner), HFD-19 (FOI), Drug and Chron files.

ZH:smj:pc:3/26/90

APPEARS THIS WAY
ON ORIGINAL

7 PAGES REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

Attachment III
p-1

Clinical diagnoses and concomitant therapy in the elderly

Subject No.	Diagnoses	Therapy: Trade name	Dose	
01	M. Parkinson	Madopar	525	mg/day
		Parlodel	10	mg/day
		Sibelium	5	mg/day
02	Stroke	Ubretid	2.5	mg/day
	Epilepsy	Phenobarbital	150	mg/day
	Hypertension	Lasix	40	mg/day
		Lasilactone	100	mg/day
03	Colon cancer (1976)	Cetiprin	400	mg/day
	Senile dementia	Distraneurin	300	mg/day
04	Hypertension	Lasix	30	mg/day
	Amaurosis	Ludiomil	75	mg/day
		Seresta	15	mg/day
		Rumatral	2x500	mg/day
05	M. Parkinson	Madopar	250	mg/day
	M. Paget	Aspirin	500	mg/day
06	M. Parkinson	Digoxin	0.125	mg/day
	Cardiac insufficiency	Madopar	375	mg/day
	Depression			
07	Venous insufficiency	Lasix	30	mg/day
	Hernia inguinalis	Melleril	200	mg/day
08	Epilepsy	Phenobarbital	100	mg/day
		Epanutin	400	mg/day
		Cetiprin	200	mg/day
09	Depression	Gutron	5	mg/day
	Orthostatic hypotension	Normiton	20	mg/day
		Hydergin	4.5	mg/day
10	Hypertension	Tegretol	600	mg/day
	Coronary disease	Lexotanil	3	mg/day
	Epilepsy	Phenobarbital	40	mg/day
		Lasix	70	mg/day
		Adalat	20	mg/day
11	M. Parkinson	Madopar	437.5	mg/day
		Dopergin	0.4	mg/day
		Gutron	5	mg/day
12	Hypertension	Digoxin	0.25	mg/day
	Angina pectoris	Moduretic	1	tabl./day
		Seresta	15	mg/day

612

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INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF SMS 201-995

after subcutaneous administration of 0.10 mg in elderly volunteers

Time [min]-> / Subject No.	0	5	10	15	30	45	60	75	90	120	150	180	210	240	300	360	420	480	600
1																			
2																			
3																			
4																			
5																			
6																			
7																			
8																			
9																			
10																			
11																			
12																			
N	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00	12.00
MEDIAN	0.00	2.04	3.45	3.74	3.63	3.50	3.38	2.97	2.71	2.44	2.10	1.83	1.43	1.17	0.94	0.65	0.59	0.45	0.29
MEAN	0.00	2.71	3.84	4.07	3.91	3.72	3.66	3.19	2.93	2.57	2.21	1.86	1.55	1.24	0.90	0.73	0.58	0.45	0.30
STDEV	0.00	1.94	1.59	1.26	0.93	0.93	1.00	0.65	0.64	0.47	0.39	0.33	0.32	0.35	0.23	0.22	0.20	0.14	0.09
SEM	0.00	0.56	0.46	0.36	0.27	0.27	0.29	0.19	0.18	0.14	0.11	0.10	0.09	0.10	0.07	0.06	0.06	0.04	0.03
L.95%CONF.LIM	0.00	1.47	2.83	3.27	3.32	3.13	3.02	2.78	2.53	2.27	1.96	1.65	1.35	1.02	0.75	0.59	0.46	0.36	0.24
U.95%CONF.LIM	0.00	3.94	4.85	4.87	4.50	4.31	4.29	3.61	3.34	2.87	2.46	2.07	1.75	1.46	1.04	0.87	0.71	0.54	0.36

Detection limit: 0.05 ng/ml , 0.05 ng/ml

INDIVIDUAL MODEL PARAMETERS OF SMS 201-995

after subcutaneous administration of 0.10 mg in elderly volunteers

Subject No.	tmax [min]	Cp(tmax) [ng/ml]	AUC(0-480) [ng/ml*min]	AUC(0-600) [ng/ml*min]	ka [1/min]	t(ka) [min]	timelag [min]	K [1/min]	t(K) [min]	AUC(Inf) [ng/ml*min]	V/F [l]	Cl/F [ml/min]
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
N	12	12.00	12	12	12.000	12.00	12.00	12.00000	12	12	12.0	12
MEDIAN	16	4.07	769	813	0.203	3.46	0.00	0.00508	137	852	25.1	118
MEAN	23	4.49	805	850	0.373	3.37	1.29	0.00500	140	888	23.5	117
STDEV	19	1.23	164	176	0.304	2.36	1.71	0.00055	16	196	4.0	24
SEM	5	0.35	47	51	0.088	0.68	0.49	0.00016	5	57	1.2	7
L.95%CONF.LIM	11	3.71	700	738	0.180	1.87	0.20	0.00465	130	764	21.0	102
U.95%CONF.LIM	35	5.27	909	961	0.666	4.86	2.37	0.00535	151	1013	26.0	133

Attach. III p 3

Attach III p-5

Pharmacokinetics of SMS 201-995 in the elderly Fig. 5

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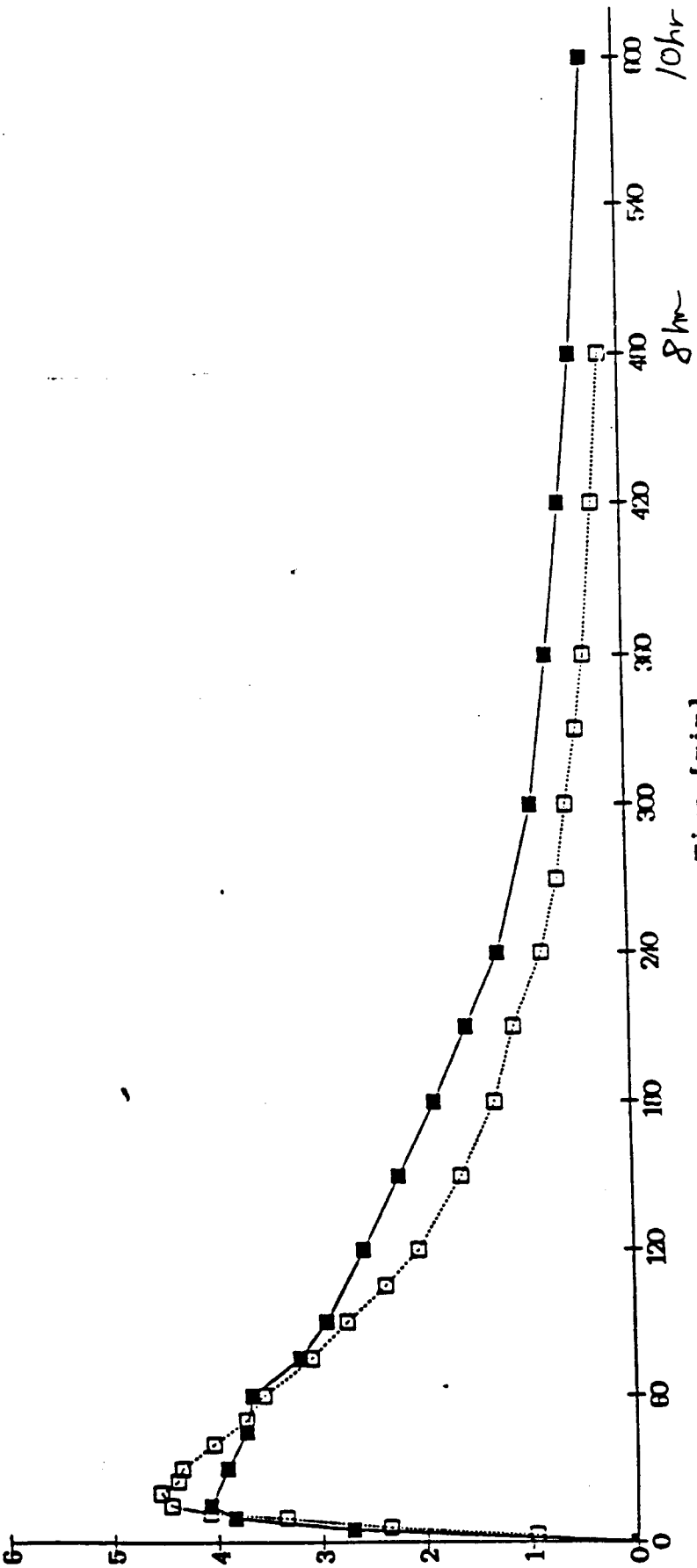
MEAN PLASMA CONCENTRATIONS [ng/ml] OF SMS 201-995

after subcutaneous administration of 0.10 mg



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019667/S004

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

OCTREOTIDE ACETATE
SANDOSTATIN® SC INJECTION
(0.2 AND 1.0 MG/ML, 5 ML MDV)
NDA 19-667 (S-004)
REVIEWER: CHARLES R. BRADLEY, PH.D.
1-S, 1-O

SANDOZ RESEARCH INS.
ROUTE 10
EAST HANOVER
NJ 07936
SUBMISSION DATES:
DECEMBER 20, 1989
AUGUST 6, 1990

MAR 8 1991

REVIEW OF BIOEQUIVALENCE STUDY AND LABELLING REVISION

I. BACKGROUND: Sandostatin® is a synthetic octapeptide analogue of human somatostatin, a tetradecapeptide. Sandostatin® has been demonstrated to be considerably more active than somatostatin in inhibiting growth hormone, insulin, glucagon, and other hormone secretions in animals as well as in humans. It has a longer duration of action than somatostatin, as the elimination half-life of somatostatin in humans is 2-3 minutes, compared to approximately 100 minutes for Sandostatin®.

The original NDA 19-667 was filed by the sponsor on February 6, 1987 and approved by the Agency on October 21, 1990. Sandostatin® is currently approved for clinical use in patients with metastatic carcinoid and vasoactive intestinal peptide-secreting tumors. Subcutaneous injection is the recommended route of administration for octreotide acetate. The initial dosage is 0.05 mg, administered SC in the deep fat. The marketed form of Sandostatin® is a 1 ml single dose ampul (SDA) available in three strengths, 50, 100, and 500 g/ml.

From the present study it seems that the sponsor is seeking approval for multiple dose vials (MDV; 5 ml) of Sandostatin with two different strengths, 0.2 and 1.0 mg/ml. The present study (Study No. 104) evaluates the bioavailability/bioequivalence of the MDV of Sandostatin® relative to the currently approved and marketed 0.5 mg/ml SDA.

* * *

II. STUDY NO. 104

A. TITLE: BIOAVAILABILITY OF SUBCUTANEOUS DOSE OF TWO STRENGTHS (0.2 MG/ML , 1 MG/ML) OF SANDOSTATIN® MULTIPLE DOSE VIALS RELATIVE TO THE MARKETED SINGLE DOSE AMPUL (0.5 MG/ML) IN HEALTHY MALE VOLUNTEERS

C. OBJECTIVE: To determine the bioavailability of two strengths (0.2 mg/ml and 1 mg/ml) of the Sandostatin® Multiple Dose Vial (MDV), experimental dosage forms, relative to the marketed Single Dose Ampul (SDA), (0.5 mg/ml), in healthy male subjects.

D. SUBJECTS: Twenty-four (24) normal healthy male volunteers were entered, where octreotide serum levels data from only 19 subjects were available for statistical analysis (See Comment No. 1). Age: Weight: Height: . Inclusion/exclusion criteria were adequately described.

E. DOSAGE FORMS:

Concentration	Single/Multiple Dose (Vial Size)	Kngl No.	Batch No.
0.5 mg/mL	Single (1 mL)	71135.01	Y239MF1286
0.2 mg/mL	Multiple (5 mL)	790-1078	6SMS 1005
1.0 mg/mL	Multiple (5 mL)	790-1116	6SMS 1008

F. STUDY DESIGN AND DRUG ADMINISTRATION: An open-label, 3-period repeated Latin square design with a 7-day washout period between consecutive drug treatments. Each subject received 0.4 mg subcutaneous dose of octreotide (as the acetate) in the deltoid muscle area as follows:

Treatment 1: 0.4 mg = 2 ml of 0.2 mg/ml MDV.
Treatment 2: 0.4 mg = 0.4 ml of 1 mg/ml MDV.
Treatment 3: 0.4 mg = 0.8 ml of 0.5 mg/ml SDA.

All subjects fasted for 10 hours prior dosing and for an additional 5 hours post-injection.

G. BLOOD COLLECTION: Samples (3 ml) were collected at 0, 5, 10, 15, 20, 25, 30, 35, 40, 50 minutes and 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, and 8 hours post-injection.

J. PHARMACOKINETICS ANALYSIS: All the reported pharmacokinetics parameters were obtained by conventional methods and/or by calculation using curve-fitting procedure (CFP) to the following equation, using the NONLIN program:

$$C_t = A[e^{-m2(t-LT)} - e^{-m1(t-LT)}]$$

where LT is the lag time, A is a constant, and m_1 and m_2 are the absorption and elimination rate constants, respectively.

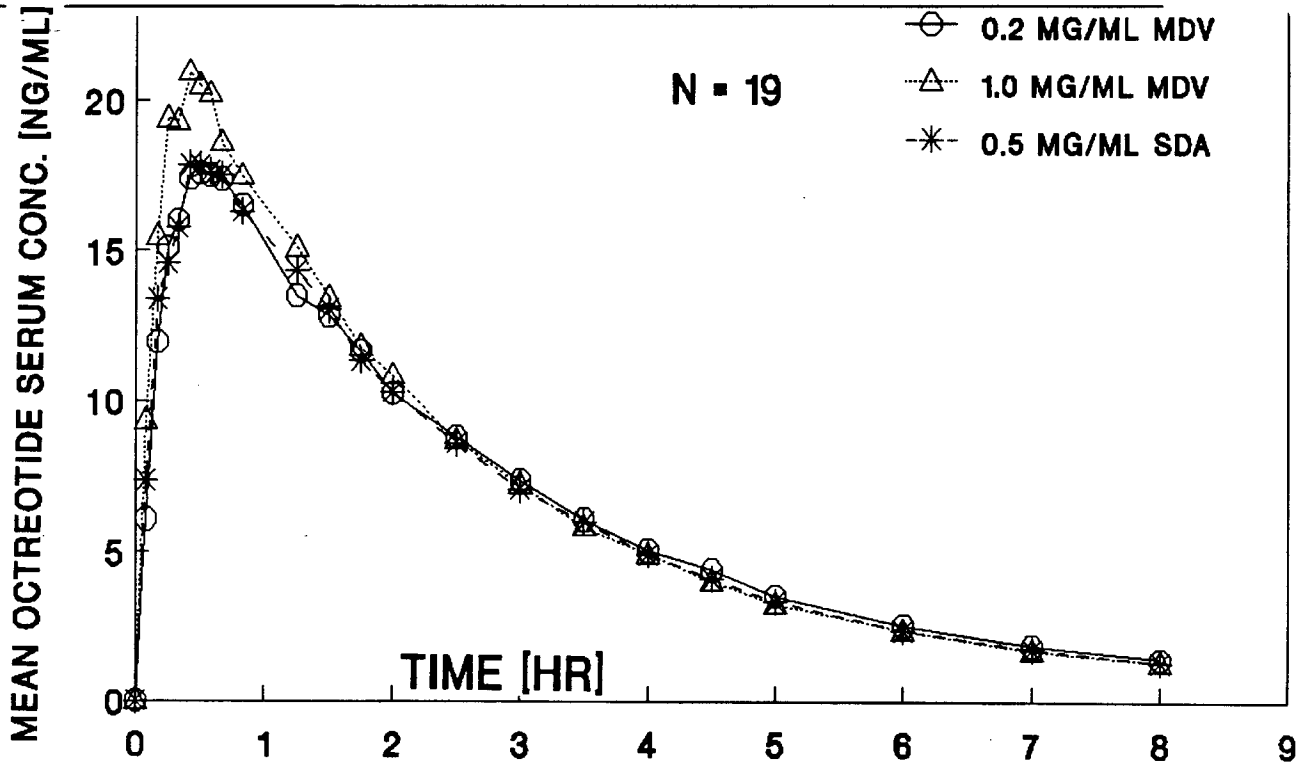
K. STATISTICAL ANALYSES: The ANOVA method and the Two One-Sided t-Test Procedure (i.e., 90% C.I.) were used to examine bioequivalence between the three treatments (See Comment No. 2).

L. RESULTS:

1. Listed in Volume 6.6 of the current submission are individual serum levels of octreotide from Labs. 1 and 2 (See Comment No. 1). Listed in Attachment II are individual pharmacokinetics parameters (calculated and curve-fitted). Following are mean serum levels of octreotide (Lab. 2) that were obtained following each treatment:

2. Mean model independent and model dependent pharmacokinetics parameters of octreotide that were obtained following each of the three treatments are tabulated in page 4. Following are the 90% confidence interval results that were obtained by using the Two One-Sided t-Test Procedure.

	90% C.I. AND CONCLUSION		
PARAMETER	0.2 mg MDV vs. 1.0 mg MDV	0.2 mg MDV vs. 0.5 mg SDA	1.0 mg MDV vs. 0.5 mg SDA
AUC	94-99 (Pass)	98-104 (Pass)	103-108 (Pass)
AUC-log	94-99 (Pass)	99-104 (Pass)	103-108 (Pass)
C_{max}	77-92 (Fail)	91-108 (Pass)	109-126 (Fail)
C_{max}-log	77-92 (Fail)	91-108 (Pass)	109-126 (Fail)
T_{max}	109-150 (Fail)	80-110 (Pass)	59-88 (Fail)
T_{max}-log	108-157 (Fail)	80-116 (Pass)	61-89 (Fail)



M. CONCLUSIONS:

1. Following S.C. administration, the 0.2 mg MDV was bioequivalent to the 0.5 mg SDA in terms of extent (AUC) and rate (C_{max} and T_{max}) of octreotide absorption.

2. Following S.C. administration, the 1.0 mg MDV was equivalent to the 0.5 mg SDA in terms of extent (AUC) but not rate (C_{max} and T_{max}) of octreotide absorption. Mean C_{max} and T_{max} values of octreotide absorption from the 1.0 mg MDV were approximately 19% and 24% higher and shorter, respectively, than those from the 0.5 mg SDA.

3. Following S.C. administration, the 0.2 mg MDV was equivalent to the 1.0 mg MDV in terms of extent (AUC) but not rate (C_{max} and t_{max}), of octreotide absorption. Mean C_{max} and t_{max} values of octreotide absorption from the 0.2 mg MDV were approximately 16% and 32% lower and longer, respectively, than those from the 1.0 mg MDV.

PARAMETER	Arithmetic Mean (± SD) (Range)		
	0.2 mg/mL MDV	1 mg/Ml	MDV 0.5 mg/ml
SDA			
Raw Data			
AUC_{0-8} (ng.hr/ml)	53.55 (7.85)	55.69 (8.60)	53.04 (8.64)
C_{max} (ng/Ml)	19.01 (4.29)	22.58 (4.66)	19.16 (3.87)
t_{max} (hr)	0.54 (0.15)	0.41 (0.12)	0.56 (0.17)
Curve-Fit Data			
$AUC_{0-\infty}$ (ng.hr/Ml)	56.83 (10.16)	56.81 (10.76)	55.46 (10.19)
C_{max} (ng/ml)	17.83 (4.06)	20.95 (3.58)	18.06 (3.64)
t_{max} (hr)	0.55 (0.18)	0.42 (014)	0.51 (0.16)
$t_{1/2,abs}$ (hr)	0.13 (0.06)	0.09 (0.04)	0.12 (0.06)
$t_{1/2,elim}$ (hr)	1.90 (0.62)	1.62 (0.34)	1.79 (0.41)
$V_{d,area}$ (Liter)	19.29 (4.14)	16.56 (2.61)	18.80 (3.45)
$V_{d,ss}$ (Liter)	20.63 (4.36)	17.50 (2.75)	20.15 (3.59)
CL_{total} (L/hr)	7.24 (1.20)	7.30 (1.48)	7.45 (1.43)

N. COMMENTS:

1. A total of 22 subjects finished the clinical portion of the study and provided complete sets of serum specimens for octreotide analysis. All specimens were first analyzed for octreotide serum levels by Lab. 1. The sponsor reported that

"However, the analysis of unknown specimens by Lab. 1 revealed much higher variability in octreotide levels than expected, based on the variability contributed by analytical method (<20% CV) and based on the previously observed intra-subject variability in bioavailability (30% CV)" and "The large discrepancies in octreotide levels between study periods, totally unexpected from previous investigations using solutions for subcutaneous administration, was therefore thought to be a logistical problem associated with analysis, such as inadvertent misassignment of study subjects, study periods, or dilution of unknown used in the assay. Such error cannot be unambiguously reconstructed, although reanalysis of the samples, under careful attention to procedure, should yield correct results. Therefore, it was decided to reanalyze the study, using all rather than only those subjects that showed high variability".

Thereafter, all serum specimens from 19 subjects, who had enough serum for reanalysis, were analyzed for octreotide levels.

2. The original layout of Study No. 104 was of 3x3 Latin square cross-over design. Because of the loss of 5 subjects, 3 due to insufficient serum volume for re-analysis in Lab. 2 and 2 who did not finish the clinical portion, the statistical analysis has to deal with unbalanced data. Accordingly, the statistical analysis was conducted for unbalanced case.

O. LABELLING CHANGES:

1. Unless the reviewing Medical Officer (HFD-510) has another opinion than Recommendation No. 3 (See Recommendation section on page 6), paragraph 2 on page 1 of the revised labelling package should be revised to exclude the 1000 mcg/ml MDV.

4/29/91 UPDATE

2. The sponsor revised sentences # 2, 3, and 4 of the first paragraph of the Pharmacokinetics subsection/CLINICAL PHARMACOLOGY section, of the approved labelling package, to read "Peak concentrations of 5.2 ng/ml (100 mcg dose) were reached 0.4 hours after dosing. Using a specific intravenous and subcutaneous doses were found to be bioequivalent". However, no statistical analysis data were provided under the current submission (as stated by the sponsor) to support the statement regarding "bioequivalence" between the intravenous and subcutaneous doses. Currently, there is no statistical support for such a statement and, therefore, the proposed statement should be revised to read the following, or something of similar content"

3. The third (3) paragraph of the Pharmacokinetics subsection was revised by the sponsor to read:

The last sentence of the above statement is not accurate regarding the increase in the half-life. Study No. SMS 4001 (bio-review dated May 22, 1990) revealed that the elimination half-life of octreotide in elderly was significantly ($p<0.01$) longer (by 46%) than that in healthy adult population. To accurately address the actual results from Study No. SMS 4001, the last sentence of the above proposed statement should be revised to read the following, or something of similar content:

4. No dose adjustment in elderly population was stated in the revised labelling package. The reviewing Medical Officer (HFD-510) was recommended in the bio-review dated May 22, 1990 to consider whether a dose adjustment is necessary in elderly population as a 46% prolongation in elimination half-life and a 25% decrease in plasma clearance of octreotide was found in this population. The reviewing Medical Officer is still recommended to consider whether dose adjustment is needed in elderly population, and if so to be stated in the labelling package.

P. RECOMMENDATIONS: The Division of Biopharmaceutics has completed reviewing Study No. 104, submitted on December 20, 1989 and August 6, 1990 under NDA 19-667. From the biopharmaceutics perspective the following are recommended:

1. Study No. 104 is acceptable.

2. Following S.C. administration, the new 0.2 mg/ml MDV was found bioequivalent to the 0.5 mg/ml marketed SDA. Therefore, the 0.2 mg/ml MDV is approvable.

3. Following S.C. administration, the new 1.0 mg/ml MDV was found equivalent to the new 0.2 mg/mL MDV and the 0.5 mg/ml marketed SDA in terms of extent (AUC) but not rate (C_{max} and t_{max}) of octreotide absorption. Therefore, the 1.0 mg/ml MDV is not approvable if rate of absorption is felt to be of clinical importance.

4. The revised labelling package is not approvable.

This Recommendation and Labelling Changes Nos. 1-3 (pages 5-6) should be conveyed to the sponsor. (NOTE: The need for labelling change No. 1 needs input from the medical officer as to whether it should be imposed.)

/S/

Charles R. Bradley, Ph.D.
Pharmacokinetics Evaluation Branch

RD initialed by John P. Hunt 3/6/91
ft initialed by John P. Hunt /S/ 3/6/91
cc: NDA 19-766, HFD-510, HFD-426 (Bradley), HFD-19 (FOI), Reviewer, Drug, and Chron files.

2 PAGES REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

RECORD OF TELEPHONE CONVERSATION/~~MEETING~~

DATE: 6/7/91

NDA NUMBER: NDA 19-667/S-004

IND NUMBER: ---

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Sandostatin (octreotide acetate)

FIRM NAME: Sandoz Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Andrew Gustafson, Ph.D.

TELEPHONE NO.: (201) 503-8703

Background: Supplement 004 for NDA 19-667 was submitted December 20, 1989 and amended August 6, 1990. All review have been completed and S-004 can be approved with labelling changes.

APPEARS THIS WAY
ON ORIGINAL

Conversation: I called Dr. Andy Gustafson on 6/7/90 to let him know the labelling changes we required for this supplement to be approved. I indicated the following:

1. In the **CLINICAL PHARMACOLOGY** sectio

2. To maintain consistency throughout the package insert, the amount of octreotide acetate in the single dose ampuls should be expressed in mcg.

Dr. Gustafson indicated that these change were acceptable to Sandoz, and committed to implement them as will be requested in the approval letter.

Andy then thanked me for my prompt follow-up on the matter.

APPEARS THIS WAY
ON ORIGINAL

SIGNATURE: /S/

DIVISION: HFD-510

FORM FD 2567 (11/77)

DIVISION FILE

U. S. GOVERNMENT PRINTING OFFICE: 1984-432-976/7126

ORIGINAL

APR 26 1991

NDA: 19,667 supplement 4
Drug: Sandostatin
Sponsor: Sandoz

Submission dates: 12/20/89, 8/6/90
Received by me: 3/26/91
Reviewed by me: 4/24/91

Subject: Bioavailability of 2 strengths (0.2 and 1 mg/ml) mutiple dose vials (MDV) relative to the marketed single dose ampule (0.5 mg/ml) in healthy male volunteers.

Method: Kinetic data was available in 19 subjects. Study design was a 3-period repeated Latin square design with a 7 day wash-out between periods. 0.4 mg of each formulation (0.2, 0.5 and 1 mg/ml) was administered sub q to each subject per period.

Results: The 0.2 mg/ml formulation was found to be bioequivalent to the 0.5 mg/ml formulation in terms of AUC, C_{max} and T_{max} (see biopharm review for specifics).

The 1 mg/ml formulation was equivalent to the 0.5 mg/ml formulation in terms of extent (AUC) but not rate of absorption (C_{max} and T_{max}):

Mean(± SD)
(Range)

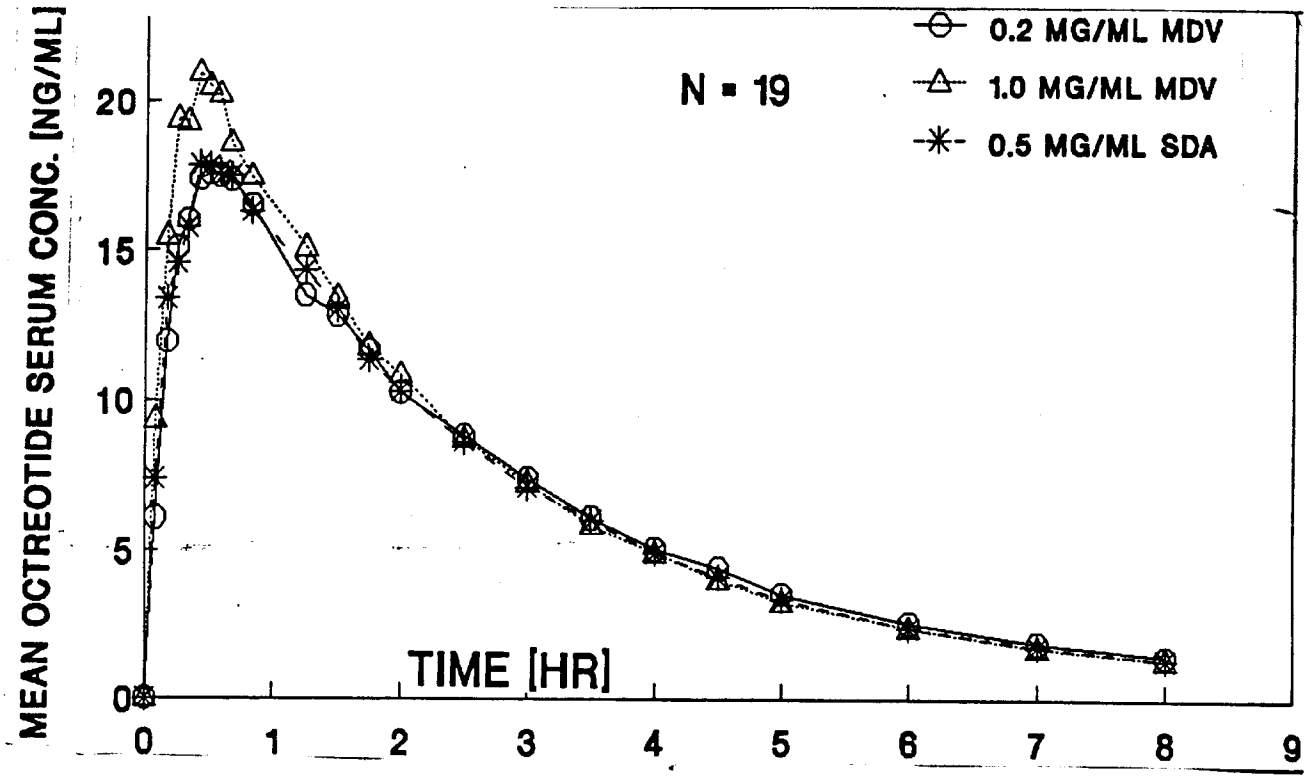
Raw Data	0.2 mg/ml	1 mg/ml	0.5 mg.ml
AUC(ng.hr/ml)	53.5(7.8)	55.7(8.6)	53.0(8.6)
C_{max}(ng/ml)	19.0(4.3)	22.6(4.7)	19.2(3.9)
T_{max}(hr)	0.54(0.15)	0.41(0.1)	0.56(0.17)

Note: Mean C_{max} and T_{max} were 18% higher and 27% lower respectively with the 1 mg/ml formulation compared to the 0.5 mg/ml formulation. Note however the considerable overlap in the ranges of these two kinetic parameters between the 1 and 0.5 mg/ml formulations.

90% confidence interval (CI) results are:

Parameter	0.2 vs. 0.5 mg/ml	1.0 vs. 0.5 mg/ml
AUC	98-104 (pass)	103-108 (pass)
AUC^{-log}	99-104 (pass)	103-108 (pass)
C_{max}	91-108 (pass)	109-126 (fail)
C_{max}^{-log}	91-108 (pass)	109-126 (fail)
T_{max}	80-110 (pass)	59-88 (fail)
T_{max}^{-log}	80-116 (pass)	61-89 (fail)

Also, serum octreotide levels were obtained from the 19 subjects up to 8 hrs. post dosing on each formulation. A plot of that data is shown on the next page:



Note: Initial analysis of the serum levels revealed large discrepancies in octreotide levels between study periods, and was thought by Sandoz to be due to a "logistical problem" such as misassignment of study subjects, study periods or dilution of unknown used in the assay. Therefore, where feasible (i.e. sufficient serum available for reanalysis), the samples were reanalyzed and the above graph represents this reanalysis.

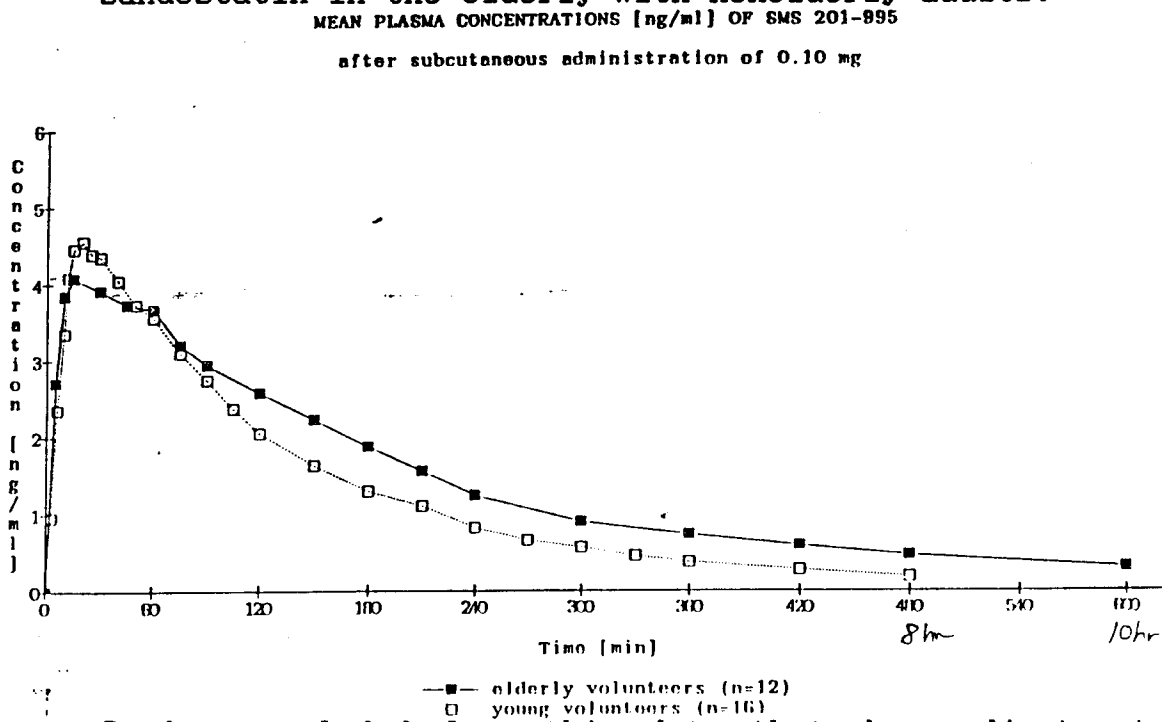
Comment re all data presented above: In view of the wide range in therapeutic dosing: 50-1500 ug/day as per the drug label, and the fact that dose is titrated according to the individual patient's response, coupled with the overlap in range values for Cmax and Tmax between the 1 and 0.5 mg/ml formulations, it seems reasonable to approve the 1 mg/ml multiple dose formulation.

Another issue pertains to the kinetics of sandostatin in the elderly. 12 elderly subjects received 100 ug sub q of a dosage form containing 0.1 mg sandostatin/ 0.1 ml. Serial blood samples were collected up to 10 hrs. post dosing. The results were compared to data previously obtained after sub q injection of 100 ug in 16 healthy adult subjects. As can be seen from the data tabulated below, AUC and the elimination half-life(t1/2) are significantly higher; and the clearance(CL/F) significantly lower in the elderly compared to nonelderly adults:

Parameter	Elderly	Adults	Significance
AUCo-sso	805±164	651±162	p< 0.05 (25%)
AUCo-inf	888±196	676±159	p< 0.01 (31%)

$t_{1/2}$ elim	140±16	96±19	p< 0.01 (46%)
CL/F	117±24	159±52	p< 0.01 (26%)

Below is a table comparing the mean plasma concentrations of sandostatin in the elderly with nonelderly adults:



Sandoz concluded from this data that dose adjustments are not necessary in the elderly. However, based on the significant differences in elimination half-life and clearance of the drug in the elderly compared to nonelderly subjects, it seems prudent that the label state that dose adjustments may be necessary in the elderly.

Regulatory Action:

1. The 0.2 and 1 mg/ml formulations are approved.
2. Agree with biopharm that the following sentence

3. Defer to biopharm regarding Sandoz' statement pertaining to bioequivalence between IV and sub q dosing routes(see biopharm review dated March 8, 1991, page 5, o.2 which states that this data was not provided in the current submission).

Note: Mr. Gustafson called today and I conveyed points 1 and 2

above to him under "Regulatory Action" but stated this had only be discussed with Dr. Troendle and approved by her. Definitive approval must await Dr. Sobel's review. I asked him to check on the dosage form of sandostatin used in the healthy adults whose kinetic parameters were compared to the elderly and to please reference the data where the IV and sub q dosing routes were compared. He said he would get back to me as soon as possible on this.

/S/

Jean Temeck, M.D.

cc. Drs. Sobel and Troendle, Dr. Bradley and Mr. Hunt (HFD-426) and Ms. Braithwaite

/S/ 4-26-91

Food and Drug Administration
Rockville MD 20857

Date December 21 1989

East Hanover NJ 07936

Attention: Hedy M. Ries

BEST POSSIBLE COPY

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Sandostatin

NDA Number: 19-667

Supplement Number: S-04

Date of Supplement: December 20, 1989

Date of Receipt: December 21, 1989

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research HFD-510
Center for Drugs and Biologics, HFN-810
Attention: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857

/S/

Supervisory Consumer Safety Officer
Division of Metabolism and Endocrine Drug Products
Center for Drugs and Biologics

cc:
NDA-File
HFN-810 File
CSO File

FORM FDA 3217c (7/84)

U.S. GOVERNMENT PRINTING OFFICE-1984-450-520/7433

Sandoz Pharmaceuticals Corporation

SANDOZ RESEARCH INSTITUTE

Drug Registration and
Regulatory Affairs

Route 10
East Hanover, New Jersey 07936
201.503.7500

December 20, 1989

NDA NO. 19-667 REF. NO. SD4

NDA SUPPL FOR SCS

Solomon Sobel, MD
Director
Division of Metabolism and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-04
Center for Drug Evaluation
and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 19-667
SANDOSTATIN® (octreotide acetate) Injection

SUPPLEMENTAL NEW DRUG APPLICATION

Dear Dr. Sobel:

Reference is made to the above cited NDA (approved October 21, 1988) for Sandostatin® (octreotide acetate) Injection and all related communications made thereto.

Enclosed find a supplement to NDA No. 19-667 which contains documentation in support of both 200 and 1000 mcg/mL 5mL multidose vial dosage forms of Sandostatin®. The currently approved dosage forms of Sandostatin® consist of 50, 100 and 500 mcg/mL 1mL ampuls.

The information contained herein describes the alternate multidose vial dosage form of the drug and consists of chemistry, manufacturing and controls documentation and draft labeling for both concentrations, together with the results of a bioavailability/bioequivalency study comparing the 200 and 1000 mcg/mL multidose vial to the approved 500 mcg/mL Sandostatin® ampul.

If you have any questions or comments, please contact Mr. Joseph Zuccarini at (201) 503-8728.

REVIEWS COMPLETED
CSO ACTION:
LETTER
/S/ 12/26/89
COMMENTS
DATE

Sincerely,

Hedy M. Ries

Hedy M. Ries
Executive Director,
Drug Registration and
Regulatory Affairs

/jek
Attachments
Submitted in duplicate

Sandoz Pharmaceuticals Corporation

SANDOZ RESEARCH INSTITUTE

Drug Registration and Regulatory Affairs

59 Route 10
East Hanover, New Jersey 07936-1951
201.503.7500

ORIGINAL

BB (505-004)

NDA ORIG AMENDMENT

August 6, 1990

Solomon Sobel, [illegible]
Director
Division of Metabolism and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-04
Center for Drug Evaluation
and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 19,667/S-004
SANDOSTATIN® (octreotide acetate) Injection

RESPONSE TO FDA REQUEST

REVIEWS COMPLETED

Noted. Date received sent to CSO ACTION:
to be reviewed by Biopharm
8/14/90 14 days
LETTER
N.A.I.
8/14/90
CONFIDENTIAL
DAT

Dear Dr. Sobel:

Please refer to our Supplemental New Drug Application (NoS S-004) for Sandostatin® (octreotide acetate) Multiple Dose Vials, submitted on December 20, 1989. In addition, please also refer to a telephone conversation between Dr. Ziad Hussein (Division of Biopharmaceutics) of the FDA and the undersigned on July 16, 1990, and a subsequent telephone conversation between Dr. Hussein and Dr. Dar-Shong Hwang of Sandoz on August 1, 1990. Dr. Hussein requested that Sandoz provide the following information regarding Study No. 204 (Bioavailability of Subcutaneous Doses of Two Strengths of Sandostatin® Multiple Dose Vials Relative to the Marketed Single Dose Ampul in Healthy Male Volunteers):

Dup sent to Biopharm

Item 1 Study No. 104 involved 24 subjects, however, octreotide serum concentration data was evaluated from only 19 of the subjects. Dr. Hussein requested that Sandoz elaborate on the justification for not evaluating data from 5 of the subjects.

Item 2a Since the data from 5 subjects was excluded from the evaluation, the statistical analysis (ANOVA) became unbalanced. Dr. Hussein wishes to repeat the statistical analysis of the data using an unbalanced ANOVA. In order to do this he requests that we provide him with the best linear unbiased estimate (BLUE), as well as the standard error of this estimate, for each treatment.

Item 2b Dr. Hussein, in his telephone conversation with Dr. Hwang of Sandoz on August 1, 1990, also requested that Sandoz provide him with "Schuirmann's" 90% confidence intervals for aid in assessing bioequivalence.

Item 3 Dr. Hussein

This information should include assay sensitivity, standard curves, as well as inter-day and intra-day precision and accuracy for each concentration reported.

A point-by-point reponse to Dr. Hussein's request is provided with this submission. If you have any comments or questions regarding the information provided, please contact me at 201-503-8703.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Andrew N. Gustafson, PhD
Manager
Regulatory Affairs

Attachments
Submitted in duplicate

APPEARS THIS WAY
ON ORIGINAL