CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21008

PHARMACOLOGY REVIEW(S)

Weber

NDA 21-008

OCT 16 1998

9 October 1998

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

Submission: 29 May, 2 Jun 98.

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

Sandostatin (octreotide acetate) LAR Depot Injection

Synthetic octapeptide analog of the tetradecapeptide somatostatin
Growth hormone, glucagon and insulin inhibitor

Recommendation: Approval [AP]

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Convey to Sponsor: Nothing from Pharmacology.

Table of Contents

NOTE: Studies in NDA 19-667 & S-017 were with Sandostatin Injection not LAR.

* Additional Reviews - Attachments: A = Original NDA 19-667 S-017 Sandostatin Injection (with Comments section from orig NDA 19-667).

* 2, 3, etc - **This NDA Review - Sandostatin LAR**
[a] [NDA 19-667 Sandostatin Injection (Review 22,24 July 87)]
[b] NDA 19-667 S-017 Sandostatin Injection (Review 25 Jun 93)
[c] IND
[d] IND

cc: Original NDA 21-008; HFD-510 NDA 21-008; HFD-345
HFD-510 RSteigerwalt, DHertig, JWeber

/S/
David H. Hertig
Pharmacologist

Concur /S/
10/16/98

Indicated Use: Sandostatin LAR is indicated for the reduction of growth hormone and IGF-1 in acromegaly, the suppression of severe diarrhea and flushing associated with malignant carcinoid syndrome and for the treatment of the profuse watery diarrhea associated with VIPoma (vasoactive intestinal peptide tumor).

Sandostatin LAR Depot Injection represents a long acting formulation whereby the active ingredient is allowing patients to receive 1 injection every month instead of the usual 60-120 injections per month [b.i.d. to q.i.d. regimen of Sandostatin Injection].

Related: IND:
NDA 19-667 (Sandostatin Injection)

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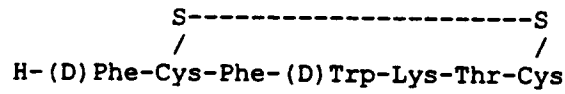
Structural Formula: SMS 201-995



H-(D)Phe-Cys-Phe-(D)Trp-Lys-Thr-Cys-Thr-ol, acetate

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-ac: $C_{49}H_{66}N_{10}O_{10}S_2 \cdot 2CH_3COOH$ MW -ac: 1139.36

Dosage Form: Microspheres consisting of octreotide acetate uniformly distributed within the biodegradable polymer, poly (DL-lactide-co-glycolide). The approximate weight ratio of octreotide to polymer is 5:95. The microsphere/mannitol blend is packaged as a sterile dry powder in 5 ml vials. Microspheres in diluent [water for injection, mannitol and sodium carboxymethylcellulose] immediately prior to injection.

Dosage: Patients not currently receiving octreotide acetate should begin therapy with Sandostatin Injection given subcutaneously. **[See Labeling]**

Acromegaly:

Patients receiving Sandostatin (octreotide acetate) Injection can be switched directly to Sandostatin LAR in a dose of 20 mg given I.M. intragluteally at 4 week intervals for 3 months. (Deltoid injections are to be avoided. Gluteal injection sites should be alternated.)

At the end of 3 months Sandostatin LAR dosage may be continued at the same level or increased or decreased based on the following regimen:

GH $\leq$ 2.5 ng/mL, IGF-I normal or near normal, and clinical symptoms controlled: maintain Sandostatin LAR dosage at 20 mg every 4 weeks.

GH > 2.5 ng/mL, IGF-I at unsatisfactory levels, and/or clinical symptoms uncontrolled, increase Sandostatin LAR dosage to 30 mg every 4 weeks.

GH $\leq$ 1 ng/mL, IGF-I normal or near normal, and clinical symptoms controlled, reduce Sandostatin LAR dosage to 10 mg every 4 weeks.

Patients whose GH, IGF-I, and symptoms are not adequately controlled at a dose of 30 mg may have the dose increased to 40 mg every 4 weeks.

Doses higher than 40 mg are not recommended.

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Carcinoid Tumors and VIPomas: **[See Labeling]**

Dosages higher than 30 mg (per 4 weeks) are not recommended because there is no information on their usefulness.

Preclinical Studies:

Effect of SMS Acetate LAR on Chronic Rejection of a Rat Kidney Allograft:
Novartis Pharma Research, Basle, Switzerland. Document 103-357 Vol 82/5-213 dtd 2 Feb 98. Non-GLP.

In the model of DA ($RT1^a$) into Lewis ($RT1^l$) rat orthotopic kidney allografting, a 14-day treatment course with cyclosporine (7.5 mg/kg/d) prevents acute cellular rejection. At about 2 months after transplantation, signs of rejection occurred as documented by magnetic resonance imaging, and graft histology. Two experiments were performed to evaluate the effect of SMS acetate LAR or placebo administered subcutaneously.

In the first experiment the test compound was administered at doses of 0.3, 3 or 30 mg/kg, two days before transplantation and about 40 days after transplantation. Doses of 3 and 30 mg/kg resulted in a decrease in the extent of rejection. A statistically significant correlation was calculated between rejection parameters and SMS dose and SMS concentrations in plasma or serum determined one week after transplantation and at autopsy, 8-23 days after the second SMS injection. The presumed stimulatory effect of IGF-1 on smooth muscle cell migration and proliferation resulting in vessel changes during chronic rejection could not be substantiated as IGF-1 concentrations showed no obvious significant correlation with rejection parameters.

In a second study SMS acetate LAR was administered at 3, 30, and 90 mg/kg 7 days before transplantation, and 28 and 65 days after transplantation; magnetic resonance imaging was performed at day 48-50 and at termination at day 102-104. Cyclosporine concentrations were determined at day 14 after transplantation; there was a negative correlation with SMS dose and SMS concentrations.

This study did not yield unequivocal conclusions with respect to the effect of SMS acetate LAR on chronic rejection. The mean level in the 90 mg/kg/SMS dose group was about half the value in the placebo-treated controls, but in the therapeutic range (420 ng/ml). The mean perfusion rate of the graft lowered in placebo-treated controls between days 48-50 and 102-104. However, an improvement was noted for the 3 and 30 mg/kg SMS dose groups. At days 102-104 SMS dose and concentration negatively correlated with the score for vessel changes in graft histology. 90 mg/kg SMS treated animals showed no improvement in graft status with regard to placebo-treated controls. According to the sponsor, this absence of a beneficial effect is explained by the pharmacokinetic interaction with cyclosporine, e.g. lowering of the cyclosporine-mediated immunological protection. Further, SMS treatment was accompanied with an SMS-dose and SMS-concentration-related reduction in levels of insulin growth factor I (IGF-I) in the circulation. This is one of the growth factors that presumably stimulate vessel changes during chronic rejection. IGF-I levels showed no significant correlation with rejection parameters, however.

The sponsor indicates that, thus, it is tempting to speculate that SMS treatment has a least some protective effect on chronic rejection of the rat kidney allograft.

Serum Levels of SMS 201-995 in the Rat after a Single S.C. Application of SMS 201-995 LAR: Document 103-271 Vol 82/5-38 dtd 26 Nov 93. Batch 100-0123,

Sandostatin LAR was given s.c. in dose levels of 3, 10 and 30 mg/kg to 5 rats per level. Blood samples were collected after 1, 2 and 6 hours, and after 2, 7 and 14 days. Thereafter, the intervals were 14 days up to day 84.

Results:

Doses of 3, 10 and 30 mg/kg gave serum levels of 4.6, 19.4 and 40 ng/ml, respectively, at 1 hour after dosing. Serum levels were fairly constant between day 7 and day 42 being in the range of 0.81, 2.4 and 8.9 ng/ml, respectively. Levels started to decline after day 42. Standard errors (SE) were 1.14 with the low dose and 1.3 with the two higher doses for day 7 to day 42.

Sandostatin serum levels (ng/ml) (ex Sponsor's Table)

	1h	6h		Day 7 to Day 42		
	Mean	Mean	% of 1h	Mean*	SE*	% of 1h
3 mg/kg	4.56	0.42	9.2	0.81	1.14	17.6
10 mg/kg	19.39	0.73	3.8	2.44	1.30	12.6
30 mg/kg	39.97	1.77	4.4	8.89	1.34	22.2

* Mean and SE: logarithmic mean of the 4 time points from Day 7 to Day 42 and its standard error factor.

In Vivo Sandostatin LAR (Acetate) Plasma Levels in the Rabbit: Report PR-1/2/4/94. Document 303-289 Vol 82/5-322 Dtd. 4 Feb 94.

Five batches of Sandostatin LAR manufactured by Stolle R&D were analyzed for this comparison: 100-3372, 100-0753, 100-0683, 100-0613, and 100-3242.
Dose: Rabbits - 15 mg SMS; Humans - 20 and 30 mg SMS (from Clinical Study E101 Report DM-1-7/30/93).
Blood samples for rabbits were taken at 0.5, 1, 2, 4, 6, 24 hrs, and at various intervals (q 3-4 days) up to 62 days.

(See next page.)

Results:
Sponsor's Table: Vol. 82/5-327
Comparison of relevant in vivo parameters in Rabbits and Humans:

Batch	3372	0753	0683	0613	3242
Release in Rabbits- 1 Day (AUC-Day 1/	77.3 µg (0.515%) 443.5 pg hr	38.80 µg (0.26%) /mL µg)	37.2 µg (0.25%)	46.44 µg (0.31%)	75.12 µg (0.53%)
Release in Rabbits- 1 Day (AUC-Day 1/	0.36% AUC-total)	0.34%	0.39%	0.37%	0.53%
Day 1 C_{max} (ng/mL): Rabbits	10.19	7.98	9.48	8.60	18.67
Release in Humans- 1 Day (AUC-Day 1/	0.42% (of 20 mg = 84 µg) 0.415% (of 30 mg = 124.5 µg) AUC-total)				
C_{max}:Humans Day 1 (ng/mL)	1.135 (20 mg) 1.510 (30 mg)				

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Reported that Batch 0613 has been analyzed in a multiple dose study in humans. These data reported to show a small burst superimposed on the drug plateau. The magnitude of the burst above the drug plateau is similar to that seen for Batch 3372.

It is further reported that for rabbits at a dose of 15 mg SMS and humans at doses of 20 mg and 30 mg SMS, the burst on the first day is quantitatively less than a single injection of 20-140 µg of Sandostatin.

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Pharmacokinetic Study Reports:

Drug Release Profiles after Single I.M. Administration in Rabbits of SMS Acetate LAR Reproducibility of the First 5 kg Sterile SMS Acetate LAR Batches Novartis Pharma AG, Basle, Switzerland
Report DMPK(CH) 1997/236 Document 203-347 Vol 88/5-2693 dtd 2 Jul 97.
Q.A. - Stated that animal experiments and bioanalytical work were conducted to conform to GLP regulations.

Using a randomized parallel design, doses of 4 mg SMS/kg body weight of Schaftenau batches 79017003, 79017005 and 79017006 and of the Medisorb batch 100-0123 (used as an internal standard) were administered intramuscularly as a single application to four female New Zealand White rabbits. Serial blood samples were collected for 72 days and plasma levels of immunoreactive SMS were determined by
Similarity was quantified by overlap of the range profile of a batch and the range profile of a pool of 13 clinical batches from as a general reference. The reproducibility of the batches was accepted by the sponsor as valid if the overlap of all batches with the general reference was $\geq$ 70%.

[The plasma levels and the AUC, C_{max} and Cp_{mean} values were corrected to a nominal dose of 4 mg/kg body weight assuming dose linearity.]

From the Sponsor's Table:

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Pharmacokinetic Characterization of SMS-LAR Forms
(index b: immediate drug release, day 0-1)
(index d: dose correction to 4 mg/kg body weight)
(index e: drug release during polymer erosion, days 2-72)

		X	Y	Z	A
AUC_d	mean	220	263	248	192
(ng.d/ml)	%cv	35	13	22	22
[days 0-69]*	sem	39	17	28	21
$Cp_{mean,d}$	mean	3.2	3.8	3.6	2.8
(ng/ml)	%cv	35.0	13.2	22.3	22.1
[days 0-69]*	sem	0.6	0.3	0.4	0.3
$C_{max,d,b}$	mean	5.7	2.9	3.3	9.0
(ng/ml)	%cv	21.1	8.2	13.5	35.9
[day 0-1]	sem	0.6	0.1	0.2	1.6
$t_{max,b}$	median	0.021	0.032	0.021	0.021
(days)	min	0.021	0.021	0.021	0.021
[day 0-1]	max	0.021	0.042	0.021	0.021
$C_{max,d,e}$	mean	8.7	14.2	10.5	8.6
(ng/ml)	%cv	25.4	49.0	25.4	20.6
[days 2-72]	sem	1.1	3.5	1.3	0.9
$t_{max,e}$	median	27	34	29	29
(days)	min	27	23	23	20
[days 2-72]	max	34	34	30	30

(* program accepted only 28 points)
X = batch 100-0123
Y = batch 79017003
Z = batch 79017005
A = batch 79017006

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Characterizing Medians are as follows:
Drug exposure — AUC_d
Immediate Drug Release — $C_{max,d,b}$

According to the sponsor, with respect to the SMS release profiles in the rabbit model, the results show a successful transfer of the SMS LAR

The SMS residue remaining in the syringes of the drug was 6.1% while that for the drug ranged from . On the other hand, the amount remaining in the vials was for the drug vs 10.9% for the drug. This suggests microparticle aggregation of the initial batches which could lead to problems in dosing.

The sponsor conducted an additional study (Doc 303-353 Vol 88/5-2794) in rabbits with the optimized form of the drug in an attempt to lessen the residue amount remaining in the syringe and vial. The

aggregation was checked in this study indirectly by measuring the SMS residues in vials after aspiration of the suspension with the syringe used for subsequent application and by monitoring the non-corrected SMS plasma levels in rabbits.

No substantial differences between the initial batch and the optimized batch in combination with SMS LAR vehicle were found concerning pharmacokinetic (dose-corrected to a nominal dose of 4 mg/kg body weight) parameters for extent (AUC) and rate (C_{max}, T_{max}) of drug exposure. Range profile-overlap values of 100% and 95% were calculated for the initial and optimized batches, respectively, using the SMS LAR vehicle, in comparison with the Medisorb reference profile. Thus, the suspendability in the SMS LAR vehicle of the optimized batch compared to the initial batch was significantly improved. However, with a sample size of only n = 4, the bioequivalence concerning the PK parameters AUC and C_{max} could not be evaluated statistically.

From Sponsor's Table:

W = batch 79017005 + SMS-LAR vehicle
Y = batch 79017012 (optimized) + SMS-LAR vehicle

	Mean		Median	
	W	Y	W	Y
AUC_c (ng.day/ml)	187	209	179	214
$Cp_{mean,d}$ (ng/ml)	2.7	3.0	2.6	3.1
$C_{max,d,b}$ (ng/ml)	2.4	2.3	2.5	2.4
$C_{max,d,e}$ (ng/ml)	7.7	10	7.6	9
$t_{max,e}$ (median days)			27	34

b = drug burst
d = values dose-corrected to 4 mg/kg

According to the sponsor, the $t_{max,e}$ value of 34 days for the optimized batch compared to 27 days for the initial batch does not influence the intended time interval for multiple dosing of once per month.

Pharmacokinetic Studies with Single Doses of SMS 201-995 (Not LAR) in Rats: Dtd November 1982. Doc 303-001 Vol 88/5-2960.

Plasma levels, urinary and fecal elimination rates and the organ distribution were measured in Han Wistar male rats after i.v. or s.c. injection of 1 mg/kg SMS 201-995. This dose was reported as a marked overdose compared to the biologically active one (the ED_{50} for the inhibition of GH-release for 1 hour in rats is 0.08 µg/kg after i.v. and s.c. administration).

From Sponsor's Tables:

Based on unchanged SMS 201-995 measured with RIA.

Plasma level	After i.v. adm.	After s.c. adm.
C_{max}	1399 ng/ml	522 ng/ml
t_{max}	15 min	45 min
t ½ α	15 min	
t ½ β	50 min	40 min
AUC (0-24h)	947.95	976.95

Elimination: Percentage of applied dose recovered (Mean ± SD) 0-72h.

Route	i.v.	s.c.
Urine	19.6 ± 4.8%	21.3 ± 2.7%
Feces	0.02 ± 0%	0.06 ± 0.04%
Total Recovery (72h)	19.6 ± 4.8%	21.3 ± 2.7%

Elimination by bile duct cannulated rats amounted to more than 100% of applied dose. This cannot be explained satisfactorily, but indicates entrance into the entero-hepatic circulation.

Tissue distribution measurements (3 rats per time period) were at 0.5, 4 and 7 hours (s.c. also 24 hours). Considerable variation was seen at 0.5 hours.

After i.v. administration, the highest drug levels were measured after 30 minutes. Maximal values were found in the kidney Most organs showed a fast elimination where drug levels declined to less than 20% of maximal within 4 hours. Target organs, pituitary, pancreas and thyroid showed a significantly slower elimination rate. SMS remained nearly constant for up to 7 hours in the pituitary.

Following s.c. administration, concentrations of SMS 201-995 at 30 minutes were generally lower than after i.v. administration. Levels remained fairly constant for at least 4 hours in most organs. Four hour levels for kidney, thyroid, liver and pancreas were 435, 199, 178 and 166 pg/mg, respectively. Some elevation was also seen in the GI tract and skin at 4 hours being 154 and 140 pg/mg respectively. Low but significant levels of SMS 201-995 were reported 24 hours later in pituitary, thyroid and bone marrow being 47, 28 and 21 pg/mg, respectively.

Muscle Concentrations of Methylene Chloride ($MeCl_2$) and Plasma Concentrations of SMS 201-995 After A Single Intramuscular Injection of SMS LAR

Report DM-1-9/13/94 dtd 13 Sep 94. Doc 303-314 Vol 88/5-2908 Non GLP.

$MeCl_2$ is a residual solvent in Sandostatin LAR microspheres.

The objective of this study was to determine the rate of disappearance of methylene chloride in rat muscle after a single i.m. injection of SMS LAR microspheres formulated with ^{14}C-methylene chloride. Muscle concentrations of radioactivity and plasma concentrations of SMS 201-995 were investigated.

Twenty-two rats each received a single i.m. injection of 30.6 mg SMS LAR microcapsules containing 1.16 mg SMS 201-995 and 0.128 mg ^{14}C-methylene chloride (0.00015 uCi/mg of into the biceps femoris muscle. [The 0, and 0.5 hour rats (#s 1-5) were misdosed.]

Approximately 3 ml serial heparinized blood samples were collected from each of two rats per time point at 0 (immediately after injection), 0.5, 1, 3, 5, 8, 24, 72, 96, 168 and 264 hours post dose. Plasma fractions were separated and stored at -20°C until analysis for SMS 201-995 by radioimmunoassay. The biceps femoris muscle (injection site) was removed at each time point, solubilized and analyzed for total radioactivity.

Muscle radioactivity rapidly declined from ca 61% of the dose at 1 hour to 18% of the dose at 5 hours, suggesting that ca 82% of the ^{14}C-methylene chloride was released within 5 hours post dose. Thereafter, the amount of radioactivity slowly declined to 11% at 24 hours and 2% at 72 hours after dose administration. By 7 days it was only ca 0.76% or less. Plasma concentrations of SMS 201-995 reached a maximum of 1026 pg/mL at 1 hour after dosing in rat #6. This value was reported to be ca 4-fold lower than the plasma concentration of SMS 201-995 previously observed at the same time point in rats receiving the same dose of SMS 201-995 microcapsules. In the previous study, half the dose was injected into each biceps femoris muscle.

Overview of Sandoz Document 303-314 (above) - Provided by Sponsor:

Doc 303-326 Vol 88/5-2936 dtd 5 Jun 95

According to this report (reported as using new in vivo data), exposure to $MeCl_2$ can be calculated on the following basis (calculations derived from the in vitro study given in parenthesis for comparison). The largest Sandostatin LAR dose form contains 30 mg Sandostatin in a deliverable dose of 723 mg* microspheres which includes a maximum of 3.6 mg $MeCl_2$ at the present control limit of 0.5%. This corresponds to a dose of 3.2 mg (2.2 mg) or 64 µg/kg (44 µg/kg) on day 1 and approximately 0.4 mg (1.4 mg) or 0.001 µg/kg/day (0.004 µg/kg/day) over the next 6 days.

As the more recent batches of Sandostatin LAR have a reduced $MeCl_2$ concentration of ca 0.25%, exposures on day one will be in the range of 32 µg/kg and for days 2-7, in the range of 0.0005 µg/kg/day.

[*Note: in the Toxicological Overview (Doc 201-282), the deliverable dose of microspheres was considered to be 630 mg and the calculations presented were based on this figure. Subsequently, the deliverable dose was calculated to be 723 mg.]

NOTE: According to the labeling -
Doses higher than 40 mg are not recommended.
Thus, new calculations are in order. - See Comments.

Toxicology:

15 Month Study - 24-Week Intramuscular Toxicity Study in Male Rats with a 39-Week Recovery Period: Study T-2942 dtd 10 May 1995. Doc. 203-323 Vol. 83/5-658 Batch 100-3372-1 Q.A. - present.

The purpose of this study was to further investigate the occurrence of a benign injection site hemangioma found in 1/5 recovery animals after 6 months of treatment and 4 months of recovery in Study T-2664 Pharm. Review of 13 Nov 91) and to identify any additional target organ toxicity.

Dose: Every 4 weeks for **24 weeks (6 injections)** with a 39 Week Recovery Phase. Vehicle - carboxymethylcellulose

Analysis of the dosing solution indicated that the delivered dose of SMS 201-995 [redacted] of the intended amount.

Dose Groups and Number of Animals:

Dose Group	SMS 201-995 mg		Number of Animals
I Control (Vehicle)	0	0	50
II Control (Placebo)	0	50	50
III Multiple Dose Toxicology	2.5	50	50
IV Multiple Dose Pharmacokinetics	2.5	50	6

[Additional rats (24 males) were included for prestudy screening and randomization purposes.]

Injection Sites: Hind limb, lower biceps femoris muscle. 0.25 mL into each hind limb.

Blood samples were collected for analysis of SMS 201-995 levels on Day 1 (24 h postdose) and during Weeks 4, 8, 12, 16, 20, 24, 32 and 36 from satellite animals. Animals (except the satellite group) were sacrificed after a 39-week recovery period and organ weights, macroscopic, and microscopic evaluations were recorded.

Group IV rats were not necropsied.

Results:

Mortality:

There was a lack of treatment correlation with mortality. Deaths included: 10 vehicle control, 7 placebo control, 5 SMS 201-995 treated.

Clinical signs:

SMS 201-995 treated rats showed a slightly higher incidence of hind leg/foot problems (primarily swollen legs/feet).

Body weight:

SMS 201-995 treated animals had lower body weights than those of controls throughout the treatment period and by the end of the treatment period were 10.2% and 11.7% lower than vehicle and placebo groups, respectively. Body weights were similar to those of controls by the end of the recovery period.

Organ Weights:

[gonads, liver, kidney, brain, heart, adrenal, thyroid, pituitary] There were no apparent drug related changes.

Macroscopic and Microscopic Changes:

A complete histopathologic processing and evaluation was done for animals in Groups I, II, and III that died prior to terminal necropsy. Findings for these rats were reported as not treatment related and appearing with equal frequency in treated and control. A limited set of tissues from each sacrificed animal in Groups I, II, and III was processed. Microscopic examination included: adrenals, bone, heart with aortic arch, injection sites, kidneys, liver, lung, lymph nodes (mesenteric, sublumbar), pancreas, pituitary, spleen, testes w/epididymides, thymus w/mediastinum, and thyroid w/parathyroids. [Blood and bone marrow smears were not evaluated since no hematological alterations were noted.] No drug related changes were reported at terminal sacrifice. A wide variety of spontaneous, background, or age-

related lesions were noted with approximately equal frequency among all groups.

No hemangiomas or target organ toxicities were found.
The incidence of wounds, cuts, scratches, hair loss or thinning was slightly greater in the SMS 201-995 animals.

Macroscopic findings in animals that died were similar to those of controls. For sacrificed animals, macroscopically the incidence of discoloration of liver lobes was slightly greater in the drug treated group (Gp I 4/40; Gp II 6/43; Gp III 10/45). The incidence of kidney discoloration was greater in the placebo group, 9/43, (without drug) vs 2/40 in controls and 3/45 in drug treated.

In general microscopic findings in animals that died or were sacrificed were similar to controls or common in rats. With regard to the skin, however, the SMS 201-995 group showed a fibrosarcoma in an animal that died and a histiocytic sarcoma in one sacrificed animal. Both findings were in the thoracic region. Acanthosis was also seen in two treated animals. It is reported that no hyperplastic or neoplastic lesions (or hemangiomas) were seen at any of the intramuscular injection sites. The incidence of myofibril degeneration of the heart was found in Groups I-III as follows: 9/40, 17/43, 6/45. 4/45 drug treated showed a hyperplastic focus of the adrenal vs 1/40 controls and 0/43 placebo treated.

Plasma Concentrations: [Limit of quantitation = 100 pg octreotide/mL plasma.] Mean plasma concentrations were sustained at a constant level from Week 1 through Week 24 (dosing weeks 1, 5, 9, 13, 17, and 21) . There did not appear to be any accumulation of drug after 24 weeks of treatment. During Week 28 (8 weeks following the last dose), the mean plasma concentration was 18% of the Week 24 value. There were no measurable plasma concentrations in Weeks 32 and 36.

Plasma Concentrations of SMS 201-995 (pg octreotide/mL plasma)
After Six Months of Monthly dosing in Rats

Week:	Predose	1(24h)	4	8	12	16	20	24	28	32	36
Mean:	0	3383	2396	2750	2409	3239	3355	2926	536	0	0
± S.D.		±1512	±954	±821	±1057	±1004	±584	±1260	±304		

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Special Studies:

DL-PLGGLU (DL-lactide-co-glycolide): T01277

Mutagenicity Test Using Salmonella Typhimurium: Study Mut.Bakt.39/93 dtd 8 Nov 94 Doc 203-318 Vol 84/5-874 DL-PLGGLU Batch 93939 Q.A. - present.

Salmonella typhimurium strains TA1535, TA97a, TA98, TA100 and TA102 were tested with either a phosphate buffer or a rat liver S9-mix.

DL-PLGGLU was dissolved and diluted in DMSO to obtain the following amounts: 1st and 3rd experiment: 3, 30, 300 and 3000 µg/plate; 2nd and 4th experiment: 150, 500 and 1500 µg/plate. Positive controls were 2-Aminoanthracene, Benzo(a)pyrene, N-Methyl-N'-nitrosoguanidine (MNNG), 9-Aminoacridine, 2-Nitrofluorene, and Mitomycin C.

DL-PLGGLU precipitated on the tester plates at 3000 µg/plate and in the fourth test also at 1500 µg/plate.

DL-PLGGLU was not bacteriotoxic up to 3000 µg/plate. DL-PLGGLU treatment did not increase the revertant numbers of any of the bacterial tester strains used.

DL-PLGGLU was devoid of mutagenic potential (up to 3000 µg/plate) under the study conditions used.

A 2-Week Intramuscular Safety Study in Rats with Impurities of Sandostatin LAR Formulation: Study T-2953. Doc. 203-284. Vol. 84/5-959 Q.A. - present.

This study was conducted to determine if the glycolide adducts (detected during the microsphere to the phenylalanine (SDZ 268-745) and lysine (SDZ 268-746), and the D- and L-lactide adducts to the phenylalanine (SDZ 269-107 and SDZ 269-108) of SMS 201-995 have an impact on toxicity and/or local tolerability of the Sandostatin LAR formulation.

Five rats/sex/group, Charles River Crl: CD BR rats were injected intramuscularly with single daily doses of test solutions for 2 weeks. One control group was injected with 0.9% saline solution at a volume of 0.5 ml/kg/day, and the other was injected with SMS 201-995 at a dose of 4 mg/kg/day. Remaining groups (4) were dosed with solutions of the impurities at 4 mg/kg/day. Injections were into the gastrocnemius muscles of alternating hind legs.

Analysis of SDZ 269-107 (Day 1, 83.7%) and SDZ 268-746 (Week 2, 74.57%) injection solutions showed values below the SOP limit. Analyses were not repeated due to lack of test compounds.

There were no unscheduled deaths or sacrifices. Treatment-related clinical signs were seen in all groups except for the vehicle control group. They included unilateral or bilateral favoring of hind limbs.

When the SMS 201-995 group was compared with that of the vehicle control group, body weight gain was lower by ca 5% for females and ca 13% for males and food consumption was reduced by ca 8% for females and 11% for males.

Reductions for SDZ 268-745 (glycolate of phenylalanine), SDZ 269-107 (d-lactide of phenylalanine), and SDZ 269-108 (l-lactide of phenylalanine) groups, were somewhat similar to that of SMS 201-995. In general mean AST and ALT values were higher (up to 2 fold) than in the vehicle control group. Red discoloration and/or hemorrhage was seen in all groups. There were some significant differences in mean absolute and relative organ weights for testes (%BW↑), liver(M↓), kidney(M wt↓), brain(M %BW↑), heart(M, SMS wt,%BrWt↓), and adrenals(F↓) compared to vehicle controls. However, there were no microscopic counterparts to the organ weight changes which were in general similar for SMS 201-995 and impurity groups. Neither sex showed any significant differences in organ weights between SMS 201-995 and impurity groups. Focal inflammatory lesions were seen in the injection sites of animals from all treatment groups, including the SMS 201-995 and vehicle control group. No marked differences in myositis were seen between SMS 201-995 and impurity groups. Both SMS 201-995 and impurity groups showed medullary plasmacytosis and/or follicular/paracortical hyperplasia in some popliteal and sublumbar lymph nodes.

In general it is reported that there was no difference in toxicity and local tolerability between SMS 201-995 and its glycolide or lactide adducts.

They thus concluded that the concentrations of 0.4% for glycolide and 0.25% for lactide adducts in SMS 201-995 were not considered to have an impact on the safety of the Sandostatin LAR formulation.

A 2-Week Intramuscular Safety Study in Rats with Impurities of Sandostatin LAR Formulation - SDZ 269-287 and SDZ 2269-288: Study T-2962
dtd 28 Apr 94. Doc. 203-285 Vol. 84/5-1220. Q.A. - present.

The purpose of this study was to determine if the **D- and L-lactide adducts to the threonine (SDZ 269-287, SDZ 269-288) of SMS 201-995** have an impact on toxicity and/or local tolerability of the Sandostatin LAR formulation. During the microsphere D- and L-lactide adducts to the threonine of Sandostatin (SMS 201-995) were detected in maximum amounts of 0.44 and 0.37%. [Solutions used in this study:

Five rats/sex/group, Charles River Crl: CD BR rats were injected intramuscularly with single daily doses of test solutions for 2 weeks. One control group was injected with 0.9% saline solution at a volume of 0.5 ml/kg/day, and the other was injected with SMS 201-995 at a dose of 4 mg/kg/day. Remaining groups (2) were dosed with solutions of the impurities at 4 mg/kg/day. Injections were into the gastrocnemius muscles of alternating hind legs.

Results:

Treatment-related clinical signs were seen in all groups except for the vehicle control group. They included unilateral or bilateral favoring of hind limbs.

Compared to controls body weight gains were lower for treated groups as follows: SMS 201-995, 15% for males and 7% for females; SDZ 269-287, 10% for males and 9% for females; SDZ 269-288, 15% for males and 8% for females.

Food consumption was also lower as follows: SMS 201-995, 12% for males, 4% for females; SDZ 269-287, 7% for males and females; SDZ 269-288, 19% for males and 8% for females.

ALT and AST values were markedly higher in the SMS 201-995 and both impurity groups (except for ALT values in SDZ 269-88 females). Compared to vehicle controls mean ALT values were increased as follows: SMS 201-995, 2-fold for males and 3-fold for females; SDZ 269-287 2-fold for males and females; SDZ 269-288, 2-fold for males. Mean AST values were higher in SMS 201-995, 5-fold for males, 7-fold for females; SDZ 269-287, 4 fold for males, 5 fold for females; SDZ 269-288, 3 fold for males, 2-fold for females. Although within historical reference range, mean alkaline phosphatase values for drug treated groups were significantly lower as were mean total protein values for females and albumin and triglyceride values for both sexes.

There were no treatment related urinalysis findings.

Compared to controls, all three compounds showed lower mean absolute and relative liver weights for males and lower absolute kidney weights for L-lactide adduct females. Mean relative kidney weights were significantly higher for SMS 201-995 and the d-lactide adduct males. Male gonad weights were also relatively higher. There were no correlations with microscopic findings in these organs.

Purple discoloration and/or hemorrhage was seen at gastrocnemius muscle injection sites in all groups including controls. One SDZ 269-287 male, and one SDZ 269-288 male and female had enlarged or discolored sublumbar lymph nodes.

There were no microscopic counterparts to organ weight changes. Injection sites of all animals including vehicle controls showed focal to multifocal inflammatory lesions. Injection myositis in the vehicle control group was subacute and ranged from trace to mild severity. In the SMS 201-995 and impurity groups it ranged from acute to subacute to chronic and ranged in severity from minimal to moderate.

No marked differences were seen in the severity of myositis between the SMS 201-995 and impurity groups.

Mutagenicity Studies of an Ingredient, Excipient, Degradates and By-Products and Octreotide Pamoate:
Salmonella Typhimurium Reverse Mutation Assay:

T 01201 (Excipient) Poly (DL-lactide-co-glycolide):

Project 158703

dtd 5 Dec 89. (Test Facility:
Doc 203-247 Vol 85/5-1418 Q.A. - present.

Salmonella typhimurium strains: TA1535, TA1537, TA1538, TA98 and TA100.

The assay was performed in two independent experiments in triplicate, using identical procedures, both with and without liver microsomal activation. Each concentration, including the controls, was tested in triplicate. The test article was tested at the following concentrations: 10.0; 100.0; 333.3; 1000.0 and 5000.0 µg/plate.

Positive Controls:

Sodium Azide, NaN_3 (10 µg/plate)
Strains TA1535, TA100

4-nitro-o-phenylene-diamine, 4-NOPD (50 µg/plate)
Strains TA1537, TA1538, TA98

2-aminoanthracene, 2-AA (10 µg/plate)
Strains TA1535, TA1537, TA1538, TA98, TA100

The S9 liver microsomal fraction was obtained from the liver of 8-12 week old male Wistar rats which received a single i.p. injection of 500 mg/kg Aroclor 1254 five days previously.

On the day of the experiment, the test article T 01201 was dissolved in acetone.

The test article precipitated weakly at 5000.0 µg/plate in the overlay agar. The undissolved particles reportedly had no influence on data recording.

Plates were incubated upside down for 72 hours at 37°C in the dark.

Colonies were counted using a If precipitation precluded automatic counting, the revertant colonies were counted by hand.

A test article was considered as a mutagen if in strain TA100 the number of reversions was at least 2x as high and in strains TA1535, TA1537, TA1538, and TA98 it was at least 3x higher compared to the spontaneous reversion rate. Also a dose-dependent increase in the number of revertants was regarded as an indication of possibly existing mutagenic potential regardless of whether the highest dose induced the above or not.

Results:

Toxic effects were manifest by a reduction in the number of spontaneous revertants, which occurred in strain TA1535 at 5000.0 µg/plate (mean of 6 vs 12 and 11 for negative and solvent control - without S9 mix) and in strain TA1537 at 1000.0 µg/plate (5 vs 11 ea for negative and solvent control - with S9 mix) and 5000.0 µg/plate (5 vs 11 each negative and solvent control with S9 mix and 3 vs 8 and 9 negative and solvent control without S9 mix). All effects were seen in experiment I.

Weak increases in the spontaneous revertant rates were observed in strain TA1535 at 1000.0 µg/plate with metabolic activation (17 vs 11 and 11 for negative and solvent control) in experiment I and in strain TA1538 at 10.0, 100.0 and 333.3 µg/plate with S9 mix (22, 23, 20 vs 19, 13 for negative and solvent control) in experiment II.

The sponsor does not consider these effects to be relevant because the effect in strain TA1535 was not reproduced in the independent experiment and the effects in strain TA1538 were due to the low level of spontaneous revertants in the corresponding solvent control.

No significant and reproducible dose-dependent increase in revertant colony numbers was noted in any of the Salmonella typhimurium strains used. Liver microsomal activation did not influence the findings.

Thus under the conditions of test, the test article did not induce point mutations by base pair changes or frameshifts in the genome of the strains used.

Mutagenicity Tests by Sandoz Pharma LTD, Basle Switzerland:

The following Mutagenicity Tests by were in general carried-out according to the protocol below:

Salmonella typhimurium strains: TA1535, TA97a, TA98, TA100 and TA102.

Drug concentrations (in DMSO): Experiment 1: 5, 50, 500 and 5000 µg/plate; Experiment 2: 500, 1500, 5000 µg/plate.

Two ml of molten agar containing 0.6% agar, 0.5% NaCl, 0.05 mM biotin and 0.05 mM L-histidine are mixed with the following components in the order given: 0.1 ml of an overnight culture (ca 10^8 cells)
0.1 ml of a test compound solution
0.2 ml of S9-mix of 0.5 ml of phosphate buffer
The mixture is poured over the surface of a minimal agar plate and allowed to harden. Three plates (one experiment 2-3 plates) are used for each concentration of the test compound, for the positive controls and the solvent. The plates are then put into a dark, 37°C incubator. After 4 days the colonies are counted and the plates checked microscopically for the presence of a light background lawn of growth.

Colony counting is performed using an unless this is made impossible by precipitation or other technical reasons.

Tests were conducted without and with an Aroclor 1254 induced rat liver homogenate S9-fraction. [Male Charles River Wiga rats 7-9 weeks old are treated with a single i.p. injection of 500 mg/kg five days before being sacrificed for liver homogenates (supernatant after centrifugation for 10 minutes at 9000 g).]

Positive Controls were: 2-Aminoanthracene (3 µg/plate - mutagenic for TA1535, TA97a, TA98, TA100, TA102); Benzo(a)pyrene (3 µg/plate - mutagenic for TA98); N-Methyl-N'-nitro-N-nitrosoqguanidine (MNNG) (3 µg/plate - mutagenic for TA1535, TA100); 9-Aminoacridine (100 µg/plate - mutagenic for TA97a); 2-Nitrofluorene (2 µg/plate - mutagenic for TA98); and Mitomycin C (0.5 µg/plate - mutagenic for TA102).

A test compound is judged by to be mutagenic in the plate test if it produces, in at least one concentration and one strain, a response equal to twice (or more) the control incidence. An exception is TA102 which has a spontaneous revertant of more than 200. For this strain an increase by a factor of 1.5 above the control levels is taken as an indication of a mutagenic effect.

APPEARS THIS WAY
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Mutagenicity Test of SDZ 268-754 (A Degradation Product of Sandostatin LAR) Using Salmonella Typhimurium:

Study Mut. Bakt. 8/94 dtd 23 Mar 94. Batch 1(1524-55-14)] Doc 203-276 Vol 85/5-1453 [SMS-1/2GLY(PHE)] Q.A. - present.

Note: Analytical data for SDZ 268-745 are incomplete and the stability of the test compound in the DMSO solvent was not determined. The expiration date of the batch used was 30 Oct 93 which is before the start of the experiments (11 Feb 94).

APPEARS THIS WAY
ON ORIGINAL

Results:

SDZ 268-754 was not bacteriotoxic and did not precipitate up to the highest concentration tested (5000 µg/plate). None of the bacterial tester strains used showed a notable increase in revertant numbers above control incidences.

It was concluded that SDZ 268-754 is devoid of mutagenic potential under the experimental conditions and standard mutagenicity criteria used.

APPEARS THIS WAY
ON ORIGINAL

Mutagenicity Test of SDZ 269-108 (A By-Product of Sandostatin LAR) Using Salmonella Typhimurium:

Study Mut. Bakt. 4/94 dtd 30 Mar 94. Batch 1(1524-128-1). Doc 203-277 Vol 85/5-1489 [L-Lactide-PHE of SMS] Q.A. - present.

Note: Analytical data for SDZ 269-108 are incomplete and the stability of the test compound in the solvent DMSO was not determined. The

expiration date of the batch used was 30 Jan 94 which is before the end of the experiments (7 Feb 94).

Results:

SDZ 269-108 was not bacteriotoxic and did not precipitate up to the highest concentration tested (5000 µg/plate). None of the bacterial tester strains used showed a notable increase in revertant numbers above control incidences.

It was concluded that SDZ 269-108 is devoid of mutagenic potential under the experimental conditions and standard mutagenicity criteria used.

Mutagenicity Test of SDZ 269-107 (A By-Product of Sandostatin LAR) Using Salmonella Typhimurium: Study Mut. Bakt. 5/94 dtd 19 Apr 94. Batch 1(1524-130-15) Doc 203-283 Vol 85/5-1525 [D-Lactide-PHE of SMS] Q.A. - present.

Note: The analytical data for SDZ 269-107 are incomplete and the stability of the test compound in the solvent, DMSO, was not determined. The expiration date of the batch used was 30 Jan 94 which was before the end of the experiments (15 Feb 94).

Results:

SDZ 269-107 was not bacteriotoxic and did not precipitate up to the highest concentration tested (5000 µg/plate). None of the bacterial tester strains used showed a notable increase in revertant numbers above control incidences.

It was concluded that SDZ 269-107 is devoid of mutagenic potential under the experimental conditions and standard mutagenicity criteria used.

Mutagenicity Test of SDZ 268-746 (A Degradation Product of Sandostatin LAR) Using Salmonella Typhimurium: Study Mut. Bakt. 6/94 dtd 5 May 94. Batch 1(1524-27-3) Doc 203-286 Vol 85/5-1561 [SMS-1/2GLY(LYS)] Q.A. - present.

Note: The analytical data for SDZ 268-746 are incomplete and the stability of the test compound in the DMSO solvent was not determined. The expiration date of the batch used was 30 Oct 93 which was before the start of the experiments (27 Jan 94).

Results:

SDZ 268-746 was not bacteriotoxic and did not precipitate up to the highest concentration tested (5000 µg/plate). None of the bacterial tester strains used showed a notable increase in revertant numbers above control incidences.

It was concluded that SDZ 268-746 is devoid of mutagenic potential under the experimental conditions and standard mutagenicity criteria used.

Mutagenicity Test of SDZ 269-287 (A By-Product of Sandostatin LAR) Using Salmonella Typhimurium: Study

Mut. Bakt. 13/94 dtd 18 May 94. Batch 1 (1524-203-20) Doc 203-288
Vol 85/5-1596 [L-Lactide-THR of SMS] Q.A. - present.

Note: The analytical data for SDZ 269-287 are incomplete and the stability of the test compound in the DMSO solvent was not determined. No expiration date was given for SDZ 269-287.

Results:

At the highest concentration tested, SDZ 269-287 was marginally bacteriotoxic for strain TA100 in the absence of the S9-mix (mean of 60 vs mean of 90 for controls for Exp.1 and 64 vs 91 for Exp.2). There was no notable increase in the revertant numbers of any of the bacterial tester strains used.

It was concluded that SDZ 269-287 is devoid of mutagenic potential under the experimental conditions and standard mutagenicity criteria used.

Mutagenicity Test of SDZ 269-288 (A By-Product of Sandostatin LAR) Using Salmonella Typhimurium: Study

Mut. Bakt. 14/94 dtd 18 May 94. Batch 1 (1524-204-18) Doc 203-287
Vol 85/5-1630 [D-Lactide-THR of SMS] Q.A. - present.

Note: The analytical data for SDZ 269-288 are incomplete and the stability of the test compound in the DMSO solvent was not determined. No expiration date was given for SDZ 269-288.

Results:

At the highest concentration tested, SDZ 269-288 was marginally bacteriotoxic for strain TA100 in the absence of the S9-mix (mean of 68 vs mean of 90 for controls in Exp.1 and 72 vs 91 for Exp.2). There was no notable increase in the revertant numbers of any of the bacterial tester strains used.

It was concluded that SDZ 269-288 is devoid of mutagenic potential under the experimental conditions and standard mutagenicity criteria used.

Studies Conducted for an Oncology Indication:

In general these studies were for comparisons of the **Acetate** and Pamoate Salt Forms of SMS (Octreotide Base) in LAR

Since these data also contain the **Acetate** in **LAR Microspheres** form of the drug, abbreviated reviews will be presented here with emphasis on the **Acetate** form of the drug rather than on a comparison with the Pamoate.

A 13-Week Toxicity in Female Rats Receiving Sandostatin LAR Intramuscularly and Tamoxifen by Oral Gavage was presented as being conducted for an Oncology Indication. Considering this study was a combination study and not for the indications subject of this NDA it will only receive a cursory review.

Acute Toxicity Studies of SMS 201-995 (not LAR or I.M.):

These studies were not formally reviewed because they were not for the to be marketed compound, Sandostatin LAR. However, information is included here for completeness.

Approximate Median Lethal INTRAVENOUS Dose of SMS 201-995 (mg/kg) in HanIbm:NMRI MICE after a 7-Day Observation Period.

Salt Form	MNLD*	Median Lethal Dose
Acetate	64	76.7

* = maximal non-lethal dose

Relevant clinical signs: sedation, tonic convulsions, lateral and ventral position, labored and accelerated breathing, ataxia and bodyweight loss. Survivors were free of toxic signs after 60 min. (acetate) No macroscopic or microscopic drug-related effects were observed.

Acute INTRAVENOUS Toxicity of SMS 201-995 Acetate in HanIbm: WIST (SPF) RATS (14 Day observation period):

LD_{50}

Both sexes = 7.85 mg/kg (95% conf. Limit. 2.79-13.30)
Males = 8.46 mg/kg
Females = 6.79 mg/kg

Relevant clinical signs: sedation, convulsions, ventral and lateral recumbency and dyspnea in male and/or females. Deaths - occurred within 1 hour after treatment.

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A 13-Week Toxicity Study in Female Rats Receiving Sandostatin LAR Intramuscularly and Tamoxifen by Oral Gavage:

Study T-3058 Doc 203-335 Vol 87/5-2327. SMS LAR Batch 101-3483-10; Tamoxifen Lot W329781H. Q.A. - present.

NOTE: **This study was carried out for an Oncology Indication - not for indications covered under this NDA.** The purpose of this study was to determine if toxicologic effects of tamoxifen are potentiated by the co-administration of Sandostatin LAR microcapsules. [Clinically only females receive tamoxifen, thus only female rats were studied.]

Emphasis will be on the SMS LAR alone group.

Dose Groups					
I	II	III	IV	V	VI
Control Placebo LAR micro-capsules	Tamoxifen 0.025 mg/kg/day	Tamoxifen 2.5 mg/kg/day	**SMS LAR 2.5 mg/month**	Tamoxifen 0.025 mg/kg/month + **SMS LAR 2.5 mg/month**	Tamoxifen 2.5 mg/kg/day + **SMS LAR 2.5 mg/month**

10 Female Sprague-Dawley [Crl:CD(SD)BR] rats per group

SMS LAR was administered by intramuscular injections once per month in Weeks 1, 5, and 9.

Tamoxifen citrate was administered daily by oral gavage for 13 Weeks.

Animals in Groups, I, II, and III received 50 mg/month placebo microcapsules which did not contain octreotide.

NOTE: The sponsor indicates that the low-dose (0.025 mg/kg/day) tamoxifen dose preparation lacked complete homogeneity , but that in general, routine dose concentration confirmation analyses (88 - 99%) were within limits.

In Weeks 1, 5, and 9 representative samples of SMS LAR dosing material were analyzed for **octreotide content** [93, 82, 71%(technical problem - reanalysis Wk 10 = 88%) of nominal amount, respectively).

Results:

There were no unscheduled deaths or treatment-related clinical signs.

Compared to controls, body weight gain from study initiation to the end of treatment was lower in all treatment groups. Low dose tamoxifen + SMS LAR resulted in a 40% reduction in body weight gain compared to 28% for tamoxifen alone or 31% for SMS LAR alone. The effect was less than additive. The high dose tamoxifen + SMS LAR produced a 64% reduction in body weight gain vs 44% for tamoxifen alone and 31% for SMS LAR alone which was less than additive.

Food consumption was slightly reduced throughout most of the treatment phase for all treated groups. Spillage was evident at various time periods.

Bloods for hematology and clinical chemistry were collected in weeks, 4, 8 and 12.

Hematology appeared to be within normal limits with no apparent toxicologically significant treatment-related findings.

Except for the low dose tamoxifen group, treated groups showed a consistent, modest increase in serum alkaline phosphatase activity. 2.5 mg/kg/day tamoxifen rats showed modest increases in calcium and inorganic phosphate levels. Inorganic phosphate levels were also increased in the 0.025 mg/kg/day tamoxifen + SMS LAR group. Decreases in cholesterol were seen with 2.5 mg/day tamoxifen alone or with SMS LAR. The sponsor reports that there were no additive or synergistic effects noted when tamoxifen was coadministered with SMS LAR.

Ophthalmoscopic and urine examinations showed no apparent drug related findings.

The low dose tamoxifen alone or with SMS LAR produced a marked decrease (ca 66%) in uterine weights; ovarian weights were decreased by ca 50%. Uterine weights of the low dose tamoxifen with or without SMS LAR were decreased ca 28%. No differences were seen in these tamoxifen-related effects with SMS LAR co-administration. Although reductions were seen in absolute adrenal and pituitary weights of the high dose tamoxifen + SMS LAR group no histopathologic correlates were seen; there was a significant reduction (64%) in body weight. Other reductions in organ weights were reported as being due to reduced body weights.

Histological examination showed the female reproductive tract to have a generalized atrophy with the high dose tamoxifen with or without SMS LAR. Ovaries were small with limited follicular activity and no corpora lutea. The mucosal epithelium of the oviducts showed cytoplasmic vacuoles or mineralization. Uterine horns were atrophic with almost no endometrial glands in the myometrium. Most rats showed vaginal epithelium with changes typical of proestrus with many mucin-secreting cells. Mammary glands appeared atrophic. The sponsor reports that there were no differences in these effects related to co-administration of SMS LAR. **There were no changes in the reproductive tracts of animals on SMS LAR alone, low dose tamoxifen or low dose tamoxifen + SMS LAR.**

Where microcapsules were administered, injection sites showed small groups of microcapsules surrounded by a sharply localized granulomatous inflammatory response. No differences in these effects were noted when SMS LAR was co-administered with tamoxifen.

White foci were occasionally noted macroscopically in the SMS LAR muscle injection sites.

Toxicokinetics: [Data From Sponsor's Tables]

Tamoxifen:

Plasma from controls showed no measurable tamoxifen concentrations and tamoxifen concentrations with 0.025 mg/kg/day with or without SMS LAR were below the limit of concentration (except 1 rat week 13). The high dose of tamoxifen without and with SMS LAR produced a C_{max} between 1 and 5 hours postdose. The presence of SMS LAR appeared to have little or no effect on the AUC or C_{max} of tamoxifen.

High dose Tamoxifen

	Tamoxifen		Tamoxifen + SMS LAR	
	Days 1-2	Week 13	Days 1-2	Week 13
AUC_{0-24} ng.h/ml	255	523	179	432
C_{max} (ng/ml)	18.2	45.7	18.5	37.4

Repeated daily dosing of 2.5 mg/kg/day tamoxifen for 13 weeks, alone or with SMS LAR resulted in tamoxifen accumulation of

SMS LAR:

Control plasma had no measurable concentration of octreotide. After a single 2.5 mg i.m. dose of SMS LAR plasma concentration peaked at 1 hour with a C_{max} of 4287 pg/ml followed by 2799 pg/ml at 24 hours. Values for like time points at Week 13 were 3678 and 2903 pg/ml.

Co-administration of 0.025 or 2.5 tamoxifen with 2.5 mg/month SMS LAR slightly reduced octreotide C_{max} and AUC values on Day 1. [Octreotide release on Day 1 originates mainly from loosely attached drug in the microspheres and does not represent true release from the microspheres, which occurs after a lag phase.]

Week 13 octreotide C_{ss} values for the low dose tamoxifen + SMS LAR were similar to that of SMS LAR alone while those for the high dose tamoxifen + SMS LAR were somewhat higher.

Plasma Octreotide Concentrations

Group	IV		V		VI	
Tamoxifen mg/kg/day	0		0.025		2.5	
SMS-ac LAR mg	2.5		2.5		2.5	
	Days 1-2	Week 13	Days 1-2	Week 13	Days 1-2	Week 13
C_{ss} (pg/ml) mean SE, n=10	-[1]	2937 225	-	3278 348	-	4207 514
T_{max} (h)	1	-	8	-	24	-
C_{max} (pg/ml)	4287	-	2767	-	2250	-
AUC_{0-24} pg.h/ml	74578	-	51574	-	43409	-
SE(AUC) pg.h/ml	10859	-	5421	-	7461	-
AUC_{0-24}/Dose pg.h/ml per mg	29831	-	20630	-	17364	-

[1] Not determined.

The sponsor concludes that repeated co-administration of 0.025 or 2.5 mg/kg/day tamoxifen for 13 weeks with 2.5 mg/month SMS LAR did not result in potentiation of toxicity or alter the target organ profiles of these compounds.

Labeling: Satisfactory. See Comments.

Comments and Conclusions: [See also Comments and Conclusion sections of attached reviews.]

Sandostatin LAR represents a product line extension of Sandostatin Injection approved (NDA 19-667 and S-017) for malignant carcinoid tumors and VIPoma on 21 October 88 and for acromegaly on 3 May 94. The active ingredient for both formulations is synthetic octreotide (SMS 201-995) which is the acetate salt of cyclic octapeptide an analog of the tetradecapeptide somatostatin. Its pharmacological properties are generally similar to those of the natural hormone somatostatin. Octreotide is reported to be an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, octreotide also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

Sandostatin LAR Depot Injection is a long acting slow release formulation in which the octreotide acetate is allowing for a single intramuscular injection every 4 weeks. The active ingredient is uniformly distributed within microspheres which are made of a biodegradable glucose star polymer, poly (DL-lactide-co-glycolide). The slow release from the site of injection occurs as the polymer biodegrades in the muscle, primarily through hydrolysis and ending up as lactic acid a normal product of muscle metabolism. Once present in the systemic circulation, octreotide distributes and is eliminated according to its known pharmacokinetic properties. Sandostatin LAR is intended for use in patients who have first been shown to be responsive to, and tolerant of, octreotide as determined by s.c. Sandostatin. [Sandostatin LAR is reportedly approved for marketing in a number of foreign countries.]

Safety of Sandostatin (octreotide) was demonstrated in a range of preclinical toxicity studies in mice, rats, rabbits, dogs, and monkeys under NDA 19,667 and S-017). These studies included acute, subchronic, chronic toxicity, and carcinogenicity studies as well as local tolerance studies, reproduction and mutagenicity studies.

For general properties and toxicity of octreotide, see attached pharmacology reviews

The following comments include findings in subject NDA 21-008.

Administration of 660 mg Sandostatin LAR microspheres containing ca 30 mg octreotide to tumor-bearing nude rats led to the inhibition of AR42J (somatostatin receptor-positive) tumor growth.

Sandostatin has previously been shown to inhibit the release of selected growth factors such as IGF-I. It also affects the proliferation of smooth muscle cells in vitro thus, the protective effect of Sandostatin LAR was studied (non-GLP) on transplant rejection parameters. Although conclusions were not unequivocal, it would appear that Sandostatin LAR might have some protective effect on chronic rejection of the rat kidney allograft.

Sandostatin LAR pharmacokinetic studies were carried out in rats and rabbits which received either single injections or 6 repeated injections at 4 week intervals. Bioavailability, as well as, the release characteristics of Sandostatin LAR were similar for the rat and rabbit studies. The small initial increase in plasma levels of octreotide (less than ca 0.6% of total drug dose in the rabbit) is believed to be due to the release of drug absorbed onto the surface of the microsphere vehicle rather than from the drug encapsulated within the delivery system. In the rat and rabbit single

injections of Sandostatin LAR produced a plateau phase lasting ca 6 weeks. In the rat multiple Sandostatin LAR injections produced plateau levels which were stabilized to those similar to a single injection. [See this review beginning p. 4.]

With respect to the SMS release profiles in the rabbit model, there appeared to be a successful transfer of the SMS LAR process.

In order to lessen the amount remaining in vials after filling syringes for injection, the manufacturing process was "optimized" by a small change in the washing procedure which involved the addition of Span 80 to the penultimate heptane wash. No substantial differences between the initial batch and the optimized batch in combination with the SMS LAR vehicle were found concerning the pharmacokinetic parameters for extent (AUC) and rate (C_{max}) of drug exposure. However, there was some difference in the T_{max} values (27 vs 34 days) in the study presented which, according to the sponsor, does not influence the intended time interval for multiple dosing of once per month.

Single dose i.m. Sandostatin LAR studies with at least 90-day observation periods were conducted in rats and rabbits. Rats received a total of 1 mg SMS 201-995 in 20 mg LAR and rabbits 25 mg SMS 201-995 in 446.4 mg LAR In general the Sandostatin LAR were well tolerated by both species. No adverse histopathological findings were seen at the muscle injection sites and there were no significant differences between the biodegradation in rats or rabbits.

Placebo and test article produced a subacute to granulomatous myositis in rats which diminished with time. Such a tissue response is reported as typically observed with many absorbable suture materials.

Pharmacokinetic characteristics of SMS 201-995 were quite similar for male rats and rabbits. Comparable blood profiles were seen with similar mg/kg intramuscular doses. The $AUC_{0-28\ days}$ was 1938 ng.hr/ml for the rabbit and 1754 and 1793 ng.h/ml for a single dose in the male rat. The AUC for the rabbit was 3676 ± 845 vs 4206 ± 878 for the rat over a 13 week period.

A multidose toxicity study was carried out in the rat Sandostatin LAR at a dose of 2.5 mg SMS 201-995 in 50 mg LAR was administered to rats as a single dose or as six monthly injections. Male rats showed a decreased body weight gain. Subacute to granulomatous myositis which greatly diminished with time, was seen with placebo and test article

A *benign hemangioma* was noted at the injection site of one of five male rats at the end of a 120 day recovery period.

In order to investigate the *benign hemangioma* finding, another six month study was carried out in which more rats (50 males) were given Sandostatin LAR (2.5 mg SMS 201-995 in 50 mg LAR i.m. once a month followed by a 39 week recovery period. A slightly greater incidence of swollen hind foot was seen with the test article. The slight decrease in body weights of the test article rats seen during the treatment phase was comparable to that of vehicle and placebo LAR controls during the recovery phase. Drug treatment showed no apparent effects on survival, clinical signs, changes in organ weights, macroscopic or microscopic observations. The hyperplastic focus of the adrenal seen in 4 treated animals vs 1 in control and none in placebo animals is unexplained. The fibrosarcoma and histiocytic sarcoma seen in the skin of one each rat of the treated group were not near the injection site but in the thoracic region.

There was no evidence of any benign hemangiomas.

There did not appear to be any accumulation of drug after 24 weeks of treatment (See this review p. 11.).

In order to support safety of the LAR formulation, special studies were also carried out which included the following:

Mutagenicity tests with various strains of Salmonella typhimurium were carried out at 1500, 3000 and 5000 µg/plate DL-PLGGLU (DL-lactide-co-glycolide microsphere material). Under the study conditions used, DL-PLGGLU was devoid of mutagenic potential i.e. the test article did not induce point mutations by base pair changes or frameshifts in the genome of the strains used.

Biodegradation/Biocompatibility of Poly(DL-lactide-co-glycolide) glucose from two different batches showed 90% biodegradation to be ca 28 days in subcutaneous skin pouches of rats.

In order to further define possible toxicity, additional studies were carried out on an ingredient, excipient, degradates and by-products of Sandostatin LAR as follows:

The LD_{50} of D,L-Lactide, a basic ingredient of the substance D,L-Poly-lactic Acid-Poly-Glycolic Acid-D-Glucose, was >2000 mg/kg in the rat after a 14-day observation period.

A 2-week intramuscular study (4 mg/kg) was conducted in rats with SMS 201-995 and impurities of the Sandostatin LAR formulation to determine if the glycolide adducts (detected during the microsphere to the phenylalanine and lysine, and the D- and L-lactide adducts to the phenylalanine of SMS 201-995 have an impact on toxicity and/or local tolerability of the SMS 201-995 formulation. Although body weights and food consumption were decreased, AST and ALT values were increased (see below) and some organ weights were affected (without microscopic counterparts), it is reported that in general there was no significant difference in toxicity and local tolerability between SMS 201-995 and its glycolide or lactide adducts. According to the sponsor, the doses of impurities were 277 times higher for glycolide adducts and 444 times higher for lactide adducts than those occurring in a double injection of 90 mg SMS 201-995. They thus concluded that the concentrations of 0.4% for glycolide and 0.25% for lactide adducts in SMS 201-995 would not have an impact on the safety of the Sandostatin LAR formulation.

A 2-week intramuscular study (4 mg/kg) was also carried out in rats with SMS 201-995, and impurities D-lactide adduct to threonine and L-lactide adduct to threonine. Compared to controls, body weight gains were lower for treated groups but within range of that of SMS 201-995. Food consumption was lower for treated also, the D-lactide having a lesser decrease and the L-lactide having a greater decrease than SMS 201-995. In general mean ALT and AST values of SMS 201-995, as well as the adducts, were markedly higher (except for ALT values of the L-lactide females) than the vehicle controls (see below). Mean absolute and/or relative organ weights showed statistically significant differences for testes, liver, and kidneys of various groups when compared to vehicle controls. There were no correlations with microscopic findings for these organs.

It is reported that the doses of impurities used in this study were 180 times higher for the D-lactide adduct and 192 times higher for the L-lactide adduct than those occurring in a double injection of 90 mg SMS 201-995. There did not appear to be any significant difference in toxicity between SMS 201-995 and its glycolate or lactide adducts.

With regard to SMS 201-995, ALT and AST values were up to 2-fold higher than that of the vehicle control group in the first adduct study (glycolide/lactide adducts). For the threonine adduct 2-week study, ALT values were 2-3-fold that of control vehicle while AST values were 5-7-fold that of the vehicle control group. The difference in findings (more

pronounced in females) in the values for the same dose of SMS 201-995 in these two 2-week studies is uncertain.

Because there was no microscopic evidence of liver damage the sponsor attributed the serum ALT and AST enzyme elevations of SMS 201-995 and impurities to injection site myositis.

Based on a daily clinical dose of 1.4 mg Sandostatin LAR (40 mg ÷ 28 days = 1.4 mg/day), the 4 mg/kg/day preclinical dose would be ca 28x the daily HTD on a surface area basis.

Bacterial Mutagenicity Studies (Ames Tests) were carried out on the following: DL-PLGGLU excipient and one of its ingredients, D,L-lactide; By-products D-lactide adduct to phenylalanine, L-lactide adduct to phenylalanine, D-lactide adduct to threonine and L-lactide adduct to threonine; Degradate products glycolate adduct to phenylalanine, glycolate adduct to lysine. Findings in these studies were negative. However, analytical data for some of the compounds was incomplete and stability of the test compound in the DMSO solvent was not determined. In addition for some of the compounds the expiration date of the batch used was before the start or end of the study. Expiration dates were not given for two compounds and were out of date by 1-2 weeks for 2 compounds and for about 3 months for 2 others. It is uncertain whether or not use of compounds with questionable expiration dates may have compromised the validity of these mutagenicity studies.
[NOTE: According to the Chemist, shelf life specifications on these compounds may be widened.]

Also for an oncology indication, a 13-week toxicity study was carried out in female rats receiving Sandostatin LAR i.m. and tamoxifen by oral gavage. [Clinically only females receive tamoxifen.] The purpose of the study was to determine if toxicological effects of tamoxifen are potentiated by co-administration of Sandostatin LAR

Low dose tamoxifen (0.025 mg/kg/day) plus SMS LAR (2.5 mg/month) resulted in a 40% reduction in body weight gain compared to 28% for tamoxifen alone or 31% for SMS LAR alone. The high dose tamoxifen (2.5 mg/kg/day) plus SMS LAR (2.5 mg/month) produced a 64% reduction in body weight gain vs 44% for tamoxifen alone and 31% for SMS LAR alone. Although these effects for both doses of the tamoxifen plus SMS LAR were greater than that of the individual compounds the effect was less than additive. The presence of SMS LAR had little or no effect on the AUC or C_{max} of tamoxifen.

Reductions of were seen in absolute adrenal and pituitary weights of the high dose tamoxifen + SMS LAR group, however, no histopathologic correlates were seen; there was a significant reduction (64%) in body weight.

Although toxicity, mainly that of tamoxifen, was evident it appears that repeated co-administration of 0.025 or 2.5 mg/kg/day tamoxifen with 2.5 mg/month SMS LAR did not result in potentiation of toxicity or alter the target organ profiles of these compounds.

Methylene chloride is found as a residual solvent in Sandostatin LAR microspheres which brings-up the concern of possible $MeCl_2$ toxicity and allowable limits. The ICH permitted daily exposure (PDE) for this Class 2 solvent is 6.0 mg/day (FR Vol. 62, No 247, 24 Dec 97 - route not specified - According to "Appendix 5. Toxicological Data For Class 2 Solvents", this PDE is based on inhalation and drinking water studies.). The control limit established for residual methylene chloride in the drug product is 0.5%. The sponsor based calculations on 30 mg Sandostatin in a delivered dose of 723 mg microspheres i.e. 723 mg x 0.5% = 3.6 mg $MeCl_2$ which is below the PDE .

However, the labeling states that: Patients whose GH, IGF-I, and symptoms are not adequately controlled at a dose of 30 mg may have the dose increased to 40 mg every 4 weeks. Thus, the amount of methylene chloride should be based on the maximum 40 mg dose. [We are given that 30 mgs are contained in a **deliverable dose** of 723 microspheres. Calculation would indicate that 40 mg would require 964 mg microspheres.] 964 mg microspheres x 0.5% would give **4.82 mg $MeCl_2$ which is within the 6.0 mg/day PDE** even if the drug were released all at once. However, if the $MeCl_2$ is released in the human as it is in the rat then 89% (4.29 mg) would be released on day 1 and 11% (0.53 mg) would be released over the next 6 days.

[A worse case scenario would be based on the maximum fill weight of the vial rather than on the delivered weight of the compound. In practice if a vial containing a 30 mg dose and a vial containing a 10 mg dose were used (total 40 mg dose) and the maximum fill weights were used (Vol. 1, 2-190) mg microspheres + mg microspheres = mg microspheres x 0.5% (residual $MeCl_2$) = mg total residual $MeCl_2$. Based on the rat the expected $MeCl_2$ release the first day would be 89% or 5.59 mg and 11% or .69 mg the next 6 days.

Although under these circumstances, the $MeCl_2$ content is somewhat marginal, one would never expect to be able to "completely" empty the vial and thus, the amount of $MeCl_2$ received should be less than the ICH PDE of 6.0 mg/day.]

APPEARS THIS WAY
ON ORIGINAL

Labeling: Labeling, a modification of approved Sandostatin Injection labeling, is satisfactory.

APPEARS THIS WAY
ON ORIGINAL

In 1993, the Division of Metabolism and Endocrine Drug Products (HFD-510) completed a review of the toxicology studies supporting Sandostatin LAR and stated that "depending upon the results of the ongoing 15-month study in rats (6 monthly injections and 9 months recovery/observation), no further preclinical studies are deemed necessary to support an NDA for Sandostatin LAR". No hemangiomas or adverse Sandostatin LAR effects were observed in this 15 month study (Doc. 203-323 see this review p. 9).

In general, the preclinical toxicological profile of Sandostatin LAR suggests that toxicity is characterized by a non-adverse inflammatory response to the microcapsules at the injection site typical to that evoked by absorbable suture material and a decrease in body weights.

Recommendation: Approval

The preclinical data support the use of Sandostatin LAR for treatment of acromegaly and the symptomatic control of carcinoid syndrome and VIPomas. Thus from the standpoint of Pharmacology, this NDA may be approved for these indications.

APPEARS THIS WAY
ON ORIGINAL

/S/

cc: Original NDA 21-008; HFD-510 NDA 21-008; HFD-345 David H. Hertig
HFD-510 RSteigerwalt, DHertig, JWeber Pharmacologist

/S/

10/16/98

APPEARS THIS WAY
ON ORIGINAL