CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213224Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	213224
Submission Date	03/28/2019
Brand Name	Bynfezia Pen
Generic Name	Octreotide Acetate
Clinical Pharmacology Reviewer	Lei He, Ph.D.
Clinical Pharmacology Team Leader (Acting)	Suryanarayana Sista, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Metabolism and Endocrinology Products
Sponsor/Authorized Applicant	Sun Pharmaceutical Industries Limited
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector
Indication	Octreotide acetate injection is proposed for the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and profuse watery diarrhea associated with Vasoactive Intestinal Peptide secreting tumors.
Dosage Regimen	The initial dosage is usually 50 mcg administered (b) (4) three times daily.

1. Executive Summary

Octreotide acetate is a long acting octapeptide and has been approved for the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors. Sun Pharmaceutical Industries Limited submitted this NDA application, NDA 213224, on March 28, 2019 for octreotide acetate injection (2.5 mg/mL, 2.8 mL) via 505(b)(2) regulatory pathway using SANDOSTATIN (octreotide acetate) Injection (0.05 mg/mL, 0.1 mg/mL and 0.5 mg/mL concentration in 1 mL single-dose ampules; 0.2 mg/mL and 1 mg/mL concentration in 5 mL multiple-dose vials) (NDA 019667), as the reference product. The proposed octreotide acetate injection (2.5 mg/mL, 2.8 mL) is to be provided in a multi-dose, variable dose disposable pen injector for subcutaneous (SC) delivery. One relative bioavailability study (Study # PKD_17_257) was conducted in healthy adult subjects to compare the proposed octreotide acetate injection and the reference drug SANDOSTATIN (octreotide acetate) Injection. Results indicated that following the single dose SC administration of the proposed octreotide acetate injection (200 mcg, 0.08 mL of 2.5 mg/mL) or the reference drug SANDOSTATIN (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL), the proposed octreotide acetate injection (2.5 mg/mL) is bioequivalent to the reference drug SANDOSTATIN (octreotide acetate) Injection (1 mg/mL).

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 213224 and finds the application acceptable from a clinical pharmacology perspective.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor conducted a randomized, open label, two treatment, two period, two sequence, single dose, crossover, relative bioavailability study, Study # PKD_17_257, in healthy adult subjects to compare the proposed octreotide acetate injection and the reference drug SANDOSTATIN (octreotide acetate) Injection. Results show that following the single dose SC administration of the proposed octreotide acetate injection (200 mcg, 0.08 mL of 2.5 mg/mL) or the reference drug SANDOSTATIN (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL), the 90% confidence intervals of the geometric mean ratios of octreotide C_{max}, AUC_{0-t}, and AUC_{0-inf} are all within 80-125% limit, indicating proposed octreotide acetate injection (2.5 mg/mL) is bioequivalent to the reference drug SANDOSTATIN (octreotide acetate) Injection (1 mg/mL).

Note that biopharmaceutical inspections were requested for both clinical site and bioanalytical site for Study # PKD_17_257. The Office of Study Integrity and Surveillance (OSIS) recommended accepting data without an on-site inspection since OSIS recently inspected the requested sites and the inspectional outcome from the inspections was classified as No Action Indicated (NAI). For more detailed information, please refer to the consult review by Dr. Folaremi Adeyemo dated June 11, 2019 in DARRTS (Date 11 June 2019, Reference ID: 4446788).

2. Question Based Review

2.1 Was bioequivalence established for the proposed octreotide acetate injection (2.5 mg/mL) and the reference drug SANDOSTATIN (octreotide acetate) Injection (1 mg/mL)?

The Sponsor submitted one relative bioavailability study, Study # PKD_17_257, entitled "*A randomized, open label, two treatment, two period, two sequence, single dose, crossover, relative bioavailability study of Octreotide acetate Injection, 2.5 mg/mL, Pen Injector, 2.8 mL of Sun Pharmaceutical Industries Ltd. and Sandostatin (Octreotide acetate) Injection 1000 mcg/mL (1 mg/mL), 5 mL Multi-dose vial of Novartis Pharmaceutical Corporation in healthy adult subjects under fasting condition*" in this NDA submission.

Study # PKD_17_257 was a randomized, open label, two treatment, two period, two sequence, single dose, crossover, relative bioavailability study in 20 healthy subjects under fasted condition (Figure 1). In each period, subjects were randomized to receive a single dose SC administration of the proposed octreotide acetate injection (200 mcg, 0.08 mL of 2.5 mg/mL) (Test, A) or the reference drug SANDOSTATIN (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL) (Reference, B). Drug administration was separated by a washout of 7 days between the 2 treatment periods.

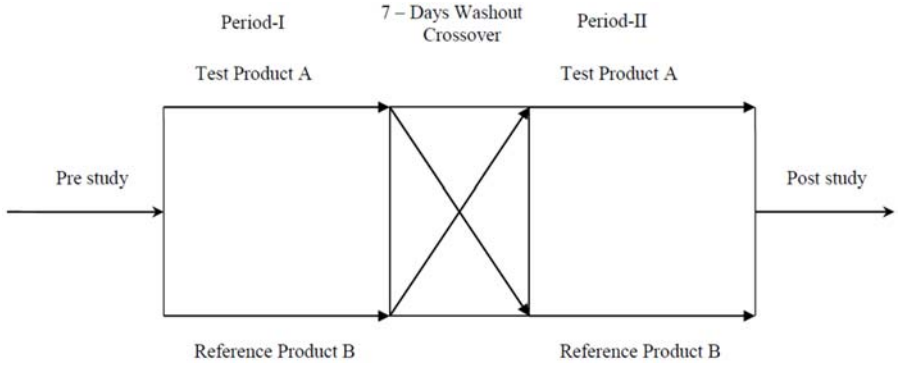

Figure 1. Study design of # PKD_17_257

- **Test (A):** Single SC dose of octreotide acetate Injection (Pen injector), 2.8 mL, 200 mcg dose (0.08 mL) (Batch Number: JKSEX570A)

- **Reference (B):** Single SC dose of SANDOSTATIN (Octreotide acetate) Injection 1000 mcg/mL (1 mg/mL), 5 mL Multidose vial, 200 mcg dose (0.2 mL) (Lot Number: S0009)

PK samples were collected pre-dose and at 0.083, 0.167, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 7, 8, and 10 hours following drug administration. Plasma concentrations of octreotide were measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay method.

A total of 20 subjects were enrolled and dosed in the study. The reason for discontinuation of one subject was listed as "One drop of blood at the injection site after dosing in period-II".

PK results from 19 completing subjects indicated that following a single dose SC administration of the proposed octreotide acetate injection (200 mcg, 0.08 mL of 2.5 mg/mL) (Test) or SANDOSTATIN (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL) (Reference), octreotide concentration-time profiles overlap (Figure 1). Statistical analysis showed that the 90% confidence intervals of the geometric mean ratios (GMR) of octreotide C_{max}, AUC_{0-t}, and AUC_{0-inf} are all within the 80-125% limits, indicating the proposed octreotide acetate injection (2.5 mg/mL) is bioequivalent to the reference drug SANDOSTATIN (octreotide acetate) Injection (1 mg/mL) (Tables 1, 2).

Note that biopharmaceutical inspections were requested for both clinical site and bioanalytical site for Study # PKD_17_257. The Office of Study Integrity and Surveillance (OSIS) recommended accepting data without an on-site inspection since OSIS recently inspected the requested sites and the inspectional outcome from the inspections was classified as No Action Indicated (NAI). For more detailed information, please refer to the consult review by Dr. Folaremi Adeyemo dated June 11, 2019 in DARRTS (Date 11 June 2019, Reference ID: 4446788).

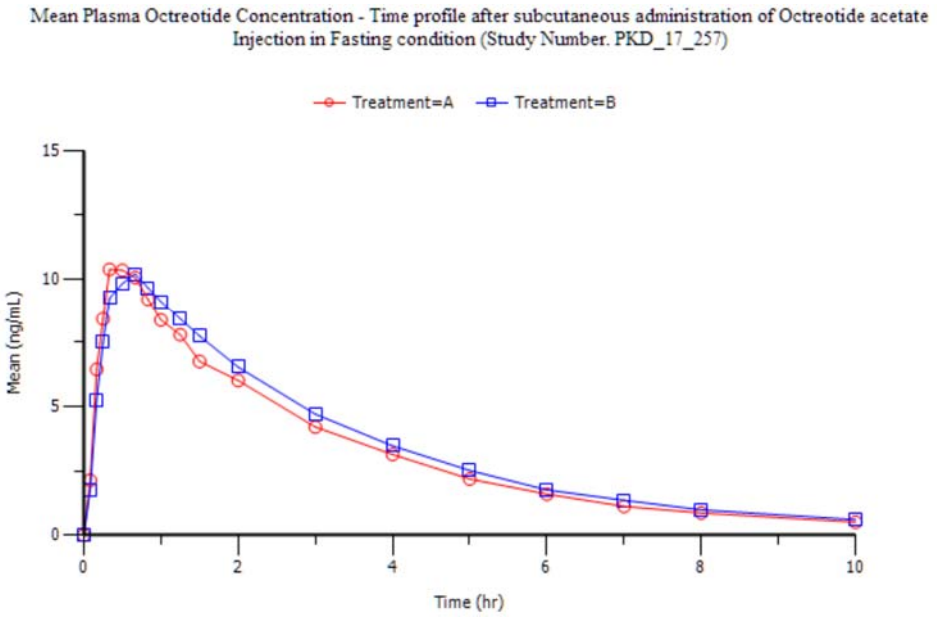

Figure 1. **Mean (+SD) octreotide concentration-time profiles after a single dose SC administration of the proposed octreotide acetate injection (200 mcg, 0.08 mL of 2.5 mg/mL) (Test, A) or SANDOSTATIN (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL) (Reference, B)**

(Source: Page 46 of Study # PKD_17_257 CSR)

Table 1. **PK parameters of octreotide after a single dose SC administration of the proposed octreotide acetate injection (200 mcg, 0.08 mL of 2.5 mg/mL) (Test) or SANDOSTATIN (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL) (Reference)**

Parameters	Octreotide acetate injection, 2.5 mg/mL, Pen Injector, 2.8 mL [0.08 mL dose] Test (A)				Sandostatin (Octreotide acetate) Injection 1000 mcg/mL (1 mg/mL), 5 mL Multi-dose vial [0.2 mL dose] Reference (B)			
	Mean	±	SD	CV%	Mean	±	SD	CV%
AUC_{0-t} (ng.h/mL)	32.4469	±	4.3094	13.28	35.0336	±	4.3440	12.40
AUC_{0-inf} (ng.h/mL)	34.2684	±	4.7656	13.91	37.0966	±	4.8843	13.17
C_{max} (ng/mL)	10.9920	±	1.8272	16.62	10.7246	±	2.0325	18.95
T_{max} (h)	0.5394	±	0.2397	44.44	0.5922	±	0.1688	28.50
T_{max}* (h)	0.500 (0.333 - 1.250)	-	-	-	0.667 (0.250 - 0.833)	-	-	-
K_{el} (h^{-1})	0.29741	±	0.05409	18.19	0.29792	±	0.02974	9.98
$t_{1/2}$ (h)	2.4078	±	0.4576	19.00	2.3506	±	0.2556	10.88
% AUC Extrapolation	5.225	±	1.888	36.14	5.466	±	1.256	22.98

*Median values (range) are presented.

Source: Appendix 16.2.6.1

(Source: Table 14.2-1A, Study # PKD_17_257 CSR)

Table 2. **Statistical analysis of the systemic exposure parameters of octreotide after a single dose SC administration of the proposed octreotide acetate injection**

(200 mcg, 0.08 mL of 2.5 mg/mL) (Test) or SANDOSTATIN (octreotide acetate) Injection (200 mcg, 0.2 mL of 1 mg/mL) (Reference)

	GeoMean (Test)	GeoMean (Reference)	90% CI of GMR (%) (Test/Reference)
C_{max} (ng/mL)	10.56	10.85	97.32 (91.60, 103.40)
$AUC_{(0-t)}$ (h·ng/mL)	34.79	32.20	108.04 (104.90, 111.25)
$AUC_{(0-inf)}$ (h·ng/mL)	36.80	33.98	108.30 (104.96, 111.75)

N=19 for each treatment.
(Reviewer's analysis)

2.2 Summary of Bioanalytical Method Validation and Performance

The measurement of octreotide concentrations in human plasma of Study # PKD_17_257 were performed using fully a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. The method summary and key descriptive parameters for the bioanalytical assay are summarized in Tables 3 and 4. All samples from Study # PKD_17_257 were analyzed within the demonstrated stability period.

Table 3. Bioanalytical method summary

Biological matrix	Human K2 EDTA Plasma
Anticoagulant	K2 EDTA
Sample volume required	300 µL
Calibration curve range of Analyte	0.100ng/mL to 19.943ng/mL
Analytical technique	Liquid chromatography
Detection mode	Tandem Mass Spectrometry
Sample treatment	Solid Phase Extraction
Quantitation method	Peak area ratio
Calibration regression	$1/X^2$
Analyte	Octreotide
MW of analyte	1019.25 g/mol
Internal standard	Octreotide D8
MW of internal standard	1027.29 g/mol

(Source: Page 11 of Bioanalytical Method Validation Report No. MV_OCT_005E)

Table 4. Summary of key descriptive parameters for octreotide bioanalytical assay used in Study # PKD_17_257

Analyte	Octreotide	
Internal Standard (IS)	Octreotide D8	
Limit of quantitation	LLOQ : 0.100ng/mL, ULOQ : 19.943ng/mL	
Relative recovery of analyte (%)	QC Low A : 86.8% QC Med B : 88.9% QC High : 87.2%	
Relative recovery of IS (%)	93.7%	
Absolute recovery of analyte (%)	QC Low A : 90.7% QC Med B : 89.9% QC High : 88.8%	
Absolute recovery of IS (%)	95.9%	
Standard curve concentrations (ng/mL)	0.100, 0.199, 1.246, 3.490, 8.476, 12.963, 15.456, 19.943 0.101, 0.201, 1.258, 3.523, 8.555, 13.084, 15.449, 19.928 (*)	
QC Concentrations (ng/mL)	Low QC A : 0.296 Low QC B : 0.887 Medium QC A : 4.509 Medium QC B : 9.520 High QC : 16.534 DQC : 35.072	Low QC A : 0.299 (*) Low QC B : 0.898 (*) Medium QC A : 4.567 (*) Medium QC B : 9.388 (*) High QC : 16.543 (*)
QC Intraday precision range (%)	0.9% to 5.3%	
QC Intraday accuracy range (%)	97.0% to 108.7%	
QC Inter day precision range (%)	0.9% to 11.8%	
QC Inter day accuracy range (%)	96.4% to 110.3%	
Bench-top stability (hrs)	11 hours at room temperature (in Plasma)	
	02 hours at room temperature (in Blood)	
Stock solution stability (days)	35 days @ 2-8°C	
Post-Processed stability (hrs)	76 hours @ 6°C	
Post Extraction Bench Top Stability (hrs)	10 hours at room temperature	
Dry Extract stability (hrs)	17 hours @ 2-8°C	
Evaporation stability (hrs)	01 hour @ 70°C	
Freeze-thaw stability (cycles)	04 cycles at -20±5°C & -65±10°C	
Long term storage stability (Days)	28 days at -20±5°C & -65±10°C	
Dilution Integrity	1.5-3 times ULOQ concentration (35.072ng/mL) diluted 5 folds.	
	% Accuracy : 1/5th : 101.0	
	% Precision : 1/5th : 3.6	
Selectivity	No significant interference observed in blank plasma samples	

(*): Freshly prepared for LT stability in Matrix Experiment

(Source: Page 10 of Bioanalytical Method Validation Report No. MV_OCT_005E)

3. Detailed Labeling Recommendations

The proposed labeling language are generally consistent with the reference product, which is acceptable from a clinical pharmacology perspective.

Side by Side comparison with Innovator for Labeling

SANDOSTATIN® (octreotide acetate) Injection, (Novartis Pharmaceuticals Corporation)		Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector (Sun Pharmaceutical Industries Limited)
Concomitant administration of Sandostatin with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.	4	**7 DRUG INTERACTIONS** **7.1 Cyclosporine** Concomitant administration of octreotide with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.
		7.2 Insulin and Oral Hypoglycemic Drugs (b) (4)
Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine.		**7.3 Bromocriptine** Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine.
Patients receiving insulin, oral hypoglycemic agents, beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents.		**7.4 Other Concomitant Drug Therapy** Patients receiving beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents.
Sandostatin has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs.		Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs.
Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormones. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine) should therefore be used with caution.		**7.5 Drug Metabolism Interactions** Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormones. Since (b) (4) octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, (b) (4) should (b) (4) be used with caution.

SANDOSTATIN® (octreotide acetate) Injection, (Novartis Pharmaceuticals Corporation)		Octreotide Acetate Injection, 2.5 mg/mL, 2.8 mL Pen Injector (Sun Pharmaceutical Industries Limited)
In patients with severe renal failure requiring dialysis, the half-life of octreotide may be increased, necessitating adjustment of the maintenance dosage.		**8.6 Renal Impairment** In patients (b) (4) dialysis, the half-life of octreotide may be increased, necessitating adjustment of the maintenance dosage.
Sandostatin substantially reduces growth hormone and/or IGF-I (somatomedin C) levels in patients with acromegaly.		**12.2 Pharmacodynamics** Octreotide substantially reduces growth hormone and/or IGF-I (b) (4) levels in patients with acromegaly.
Single doses of Sandostatin have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In controlled clinical trials the incidence of gallstone or biliary sludge formation was markedly increased (*see WARNINGS*).		Single doses of octreotide have been shown to inhibit gallbladder contractility and to decrease bile secretion in normal volunteers. In (b) (4) clinical trials the incidence of gallstone or biliary sludge formation was markedly increased *[see Warnings and Precautions (5* (b) (4)
Sandostatin suppresses secretion of thyroid stimulating hormone (TSH).		Octreotide suppresses secretion of thyroid stimulating hormone (TSH).
Pharmacokinetics After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.2 ng/mL (100-mcg dose) were reached 0.4 hours after dosing. Using a specific radioimmunoassay, intravenous and subcutaneous doses were found to be bioequivalent. Peak concentrations and area under the curve values were dose proportional after intravenous single doses up to 200 mcg and subcutaneous single doses up to 500 mcg and after subcutaneous multiple doses up to 500 mcg t.i.d. (1500 mcg/day).		**12.3 Pharmacokinetics** After subcutaneous injection, octreotide is absorbed (b) (4) and completely from the injection site. Peak concentrations of 5.2 ng/mL (100 mcg dose) were reached 0.4 hours after dosing. (b) (4) (b) (4) Peak concentrations and area under the curve values were dose proportional after (b) (4) subcutaneous single doses up to 500 mcg and after subcutaneous multiple doses up to 500 mcg three times a day (1,500 mcg/day).

In healthy volunteers the distribution of octreotide from plasma was rapid ($t_{\alpha 1/2}$ = 0.2 h), the volume of distribution (Vd_{ss}) was estimated to be 13.6 L, and the total body clearance ranged from 7 L/hr to 10 L/hr. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin. The elimination of octreotide from plasma had an apparent half-life of 1.7 to 1.9 hours compared with 1-3 minutes with the natural hormone. The duration of action of Sandostatin is variable but extends up to 12 hours depending upon the type of tumor. About 32% of the dose is excreted unchanged into the urine. 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. In patients with acromegaly, the pharmacokinetics differ somewhat from those in healthy volunteers. A mean peak concentration of 2.8 ng/mL (100-mcg dose) was reached in 0.7 hours after subcutaneous dosing. The volume of distribution (Vd_{ss}) was estimated to be 21.6 ± 8.5 L and the total body clearance was increased to 18 L/h. The mean percent of the drug bound was 41.2%. The disposition and elimination half-lives were similar to normals. In patients with renal impairment the elimination of octreotide from plasma was prolonged and total body clearance reduced. In mild renal impairment (Cl_{CR} 40-60 mL/min) octreotide $t_{1/2}$ was 2.4 hours and total body clearance was 8.8 L/hr, in moderate impairment (Cl_{CR} 10-39 mL/min) $t_{1/2}$ was 3.0 hours and total body clearance 7.3 L/hr, and in severely renally impaired patients not requiring dialysis (Cl_{CR} <10 mL/min) $t_{1/2}$ was 3.1 hours and total body clearance was 7.6 L/hr. In patients with severe renal failure requiring dialysis, total body clearance was reduced to about half that found in healthy subjects (from approximately 10 L/hr to 4.5 L/hr).	4	In healthy volunteers the distribution of octreotide from plasma was rapid ($t_{\alpha 1/2}$ = 0.2 h), the volume of distribution (Vd_{ss}) was estimated to be 13.6 L, and the total body clearance ranged from 7 L/hr to 10 L/hr. In blood, the distribution into the erythrocytes was found to be negligible and about 65% was bound in the plasma in a concentration-independent manner. Binding was mainly to lipoprotein and, to a lesser extent, to albumin. The elimination of octreotide from plasma had an apparent half-life of 1.7 to 1.9 hours compared with 1-3 minutes with the natural hormone. The duration of action of octreotide injection is variable but extends up to 12 hours depending upon the type of tumor. About 32% of the dose is excreted unchanged into the urine. (b) (4) (b) (4) In patients with acromegaly, the pharmacokinetics differ somewhat from those in healthy volunteers. A mean peak concentration of 2.8 ng/mL (100 mcg dose) was reached in 0.7 hours after subcutaneous dosing. The volume of distribution (Vd_{ss}) was estimated to be 21.6 ± 8.5 L and the total body clearance was increased to 18 L/h. The mean percent of the drug bound was 41.2%. The disposition and elimination half-lives were similar to normals. In patients with renal impairment the elimination of octreotide from plasma was prolonged and total body clearance reduced. In mild renal impairment (Cl_{CR} 40-60 mL/min) octreotide $t_{1/2}$ was 2.4 hours and total body clearance was 8.8 L/hr, in moderate impairment (Cl_{CR} 10-39 mL/min) $t_{1/2}$ was 3.0 hours and total body clearance 7.3 L/hr, and in severely renally impaired patients not requiring dialysis (Cl_{CR} <10 mL/min) $t_{1/2}$ was 3.1 hours and total body clearance was 7.6 L/hr. In patients with severe renal failure requiring dialysis, total body clearance was reduced to about half that found in healthy subjects (from approximately 10 L/hr to 4.5 L/hr).
Patients with liver cirrhosis showed prolonged elimination of drug, with octreotide $t_{1/2}$ increasing to 3.7 hr and total body clearance decreasing to 5.9 L/hr, whereas patients with fatty liver disease showed $t_{1/2}$ increased to 3.4 hr and total body clearance of 8.2 L/hr.		Patients with liver cirrhosis showed prolonged elimination of drug, with octreotide $t_{1/2}$ increasing to 3.7 hr and total body clearance decreasing to 5.9 L/hr, whereas patients with fatty liver disease showed $t_{1/2}$ increased to 3.4 hr and total body clearance of 8.2 L/hr.

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