CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-222

PHARMACOLOGY REVIEW

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA
Division of Anti-Infective Drug Products, HFD-520

NDA 21-222 (000)

KEY WORDS: SPECTRACEF, Cefditoren, ME1207

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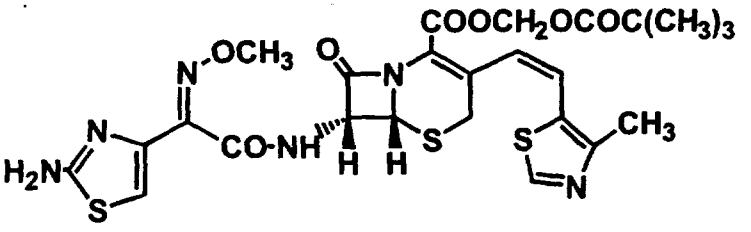
Relevant INDs: [redacted]

Drug:

Code name: ME1207
Generic name: Cefditoren pivoxil
Trade name: SPECTRACEF
Chemical name: (-)-(6R,7R)-2,2-dimethylpropionyloxymethyl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
Molecular formula: $C_{25}H_{28}N_6O_7S_3$
Molecular weight: 620.73
Structure:



A solution of ME1206 powder in distilled water was administered intraperitoneally to juvenile Sprague-Dawley rats (6/sex/group) in a single dose of either 0 (control) or 2000 mg/kg. One group of rats was three days old, and another group was 21 days old. The animals were observed for 14 days after dosing.

There were no deaths or signs of toxicity in the study.

Acute Oral Toxicity Study in Juvenile Dogs

Six male beagle puppies, three weeks of age, were used in this study. The six dogs were divided into three groups of two animals each. ME1207 granules were administered orally in gelatin capsules in a single dose of either 125, 250, or 500 mg/kg. The dogs were observed for 14 days, and then necropsied.

No dogs died in the study. Soft, mucous or watery feces were seen in every group. The test article was observed in the feces in each group, indicating that the compound had not been completely absorbed. No other effects were seen that could be attributed to treatment.

Four-week Multiple-dose Studies

Numerous studies of 28 days duration were conducted using different forms of the test substance, different routes of administration (oral and intravenous), different species (rats and dogs), and using adult and juvenile animals. Although some effects appeared consistently across studies, the incidences of other effects were quite variable. For example, some effects were seen in only one animal in a treatment-group, but not in any other animals from the same group; some effects occurred in low- and mid-dose groups, but not in the high-dose group; and sometimes effects were observed in one gender, but not in both sexes. Also, in some cases, certain serum chemistry parameters that were decreased in some studies, were found to be increased in other studies. Numerous 28-day studies in rats and dogs, by both the oral and intravenous routes, are described in this section (along with reports of 28-day oral studies in juvenile rats and dogs.

Twenty-eight-day Oral Toxicity Studies in Rats

Cefditoren pivoxil was suspended in 0.1% carboxymethylcellulose, and administered orally to Sprague-Dawley rats by gavage for 28 days. The animals were approximately six weeks of age at the start of the studies. The doses were 0, 125, 250, 500, or 1000 mg/kg/day in the definitive study, and included a 2000 mg/kg/day group in a secondary study.

Evaluations for treatment-related effects were based on clinical observations, body weights, food and water consumption, ophthalmic examinations, auditory tests, hematology, coagulation, serum chemistry, urinalysis, organ weights, and gross and microscopic histopathology.

There were no deaths in these studies. Many of the effects described in the following tables are considered to be incidental findings, because they occurred in very low incidences, or because they did not occur in both sexes, or in all studies.

The clinical chemistry changes seen at doses of 500 mg/kg/day and higher, were suggestive of subtle hepatic and renal effects. Hepatic focal necrosis, and renal tubular degeneration and necrosis were seen in one of ten animals from the 2000 mg/kg/day group.

Cecal distention was observed in all of the rat studies, and this effect is thought to be due to alteration of the bacterial flora in the intestine, by the antibiotic.

The results of several 28-day studies in young adult rats (age 5-6 weeks at the start of dosing), using different forms of the test substance, are presented in the following five tables.

Bulk Drug Substance

DOSES (MG/KG/DAY)	0	125	250	500	1000
M/F	10/10	10/10	10/10	10/10	10/10
Deaths	0	0	0	0	0
Clinical Signs	---[1]	Large, moist feces from Day 4 to the end of the study in all animals in all test groups			
Body Weight Gain	---	---	---	---	---
Food Consumption	---	↑ sporadically in all treated groups			
Water Consumption	---	↑	↑	↑	↑
Ophthalmology and Audiometry	---	---	---	---	---
Hematology	---	Decreased platelets in males in all treatment groups. Decreased neutrophils and lymphocytes in females in all treatment groups.			
Blood Chemistry	---	↓ Creatinine, total protein and globulin (M). ↓ Globulin, glucose and Ca (F)	↓ Creatinine, total protein and globulin, ↑ Na and A/G ratio (M). ↓ Globulin, glucose and Ca (F). ↑ A/G (F).	↓ Creatinine, total protein and globulin, ↑ Na and A/G ratio (M). ↑ AST and ALT (M). ↓ Globulin, protein, glucose and Ca (F)	↓ Creatinine, total protein and globulin, ↑ Na and A/G ratio (M). ↑ AST (M) & ALT (M/F). ↓ Globulin, protein, glucose & Ca (F). ↑ A/G (F).
Urinalysis	---	↓ Na	↓ Na	↓ Na; ↓ pH (M)	↓ Na; ↓ pH (M)
Necropsy	---	Cecum distended in ~1/2 of rats	Cecum distended in most rats	Cecum distended in most rats	Cecum distended in most rats
Organ Weights	---	Various changes in organ weights but none considered to be drug treatment-related			
Histology	---	---	---	---	---
Electron microscopy	---	---	---	---	---
[1] --- No abnormal findings					

Crystalline ME1207 Bulk Drug Substance

DOSES (MG/KG/DAY)	0	250	500	1000

Animals/Grp/ M/F	10/10	10/10	10/10	10/10
Deaths	0	0	0	0
Clinical Signs	---[1]	Loose stool in almost all treated animals between days 3 and 7		
Body Weight Gain	---	---	---	---
Food Consumption	---	temporary ↑ in 250 and 1000 mg/kg groups		
Water Consumption	---	↑ (M, F)	↑ (M)	↑ (M,F)
Ophthalmology and Audiometry	---	---	---	---
Hematology	---	---	↓Ht, Hb (M, F)	↓Hb & MCHC (M)
Blood Chemistry	---	----	↑ total protein and creatinine	↑in glucose and ↑ in leucine aminopeptidase
Urinalysis	---	---	↑Na &K (M) ↓ pH, Sp.Gr. (M)	↑Na &K (M), ↓Na (F)↓ pH (M, F)
Necropsy	---	Cecum distended in half of rats	Cecum distended in all rats	Cecum distended in all rats; Dilated cerebral ventricle (one animal)
Organ Weights	---	Comparable to controls		
Histology	Thyroid & stomach mucosa changes in 1 animal	Not done	Not done	Cerebral ventricle dilation in one animal; Focal pneumonia in one animal; Other minor changes

[1] --- = No abnormal findings

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Amorphous ME1207 Bulk Drug Substance

DOSES (MG/KG/DAY)	0	250	500	1000
Animals/Grp/ M/F	10/10	10/10	10/10	10/10
Deaths	0	0	0	0
Clinical Signs	---[1]	Loose stool in almost all treated animals between days 3 to the end of study		
Body Weight Gain	---	---	---	---
Food Consumption	---	↑(M) ↓(F)	↓(M, F)	---
Water Consumption	---	↑ (M, F)	↑ (M, F)	↑ (M,F)
Ophthalmology and Audiometry Effects	---	---	---	---
Hematology	---	↓Segmented neutrophils (F) ↓Lymphocytes (F)	↓Platelets (M),	↓Segmented neutrophils (F)
Blood Chemistry	---	↓ Total proteins (M,F)	↑ Total protein (F), ↓Chloride (F)	↓ Total proteins (M,F), ↓Chloride (F), ↓Glucose (M, F)
Urinalysis	---	↓pH (M,F) and Na (M).	↓ pH (M, F) and Na (M)	↓ Na (M,F) ↓ pH (M, F), ↓ K (F)
Necropsy	---	Enlarged cecum (M,F)	Enlarged cecum (M,F)	Enlarged cecum (M,F), Smaller testes, epididymis in one animal
Organ Weights	---	No dose-related effect when evaluated together for both the absolute and body wt-relative change in weight		
Histology	Focal necrosis of hepatocytes (one animal)	Not done	Not done	Atrophied seminiferous tubules, Interstitial cell proliferation in testes, fewer sperms in epididymis of one animal only, vacuolation in hepatocytes in the same animal

[1] --- = No abnormal findings

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ME1207 Granules (with citrate for three-layer tablet)

DOSES (MG/KG/DAY)	0	2000
Animals M/F	10/10	10/10
Deaths	0	0
Clinical Signs	---[1]	↑ defecation Salivation after dosing
Body Weight Gain	---	↓ (M) Day 26; ↑ (F) Days 8-22)
Food Consumption	---	↓ (M/F) Week 1
Urine Volume	---	---
Ophthalmology	---	---
Hematology	---	---
Blood Chemistry	↑ AST	↑CPK; ↓Total protein; ↓Glucose (M/F) ↑ AST(M/F) ↑ALT (M/F) ↑ creatinine (M)
Urinalysis	---	Anuria (1M);↓ pH
Necropsy	enlarged kidneys (4M)	Enlarged cecum
Organ Weights	---	Liver ↓ (M), ↑(F); ↑ kidney, testes, uterus, adrenal
Histology	Focal tubular change (7M), Calcification in (4 M)	Renal necrosis & degeneration of proximal tubules with cast (1M); Hepatic focal necrosis (1M)

[1] --- No abnormal findings

ME1207 Granules (for single-layer tablet)

DOSES (MG/KG/DAY)	0	125	250	500	1000
Animals/grp. M/F	10/10	10/10	10/10	10/10	10/10
Deaths	0	1M on Day 24	0	0	0
Clinical Signs	---[1]	Loose stool in males of all dose groups and females of 250 and 1000 mg/kg dose groups			
Body Weight Gain	---	---	---	---	---
Food Consumption	---	A decrease was noted on Day 2 in all males and females of the ≥500 mg/kg dose groups			
Ophthalmology	---	---	---	---	---
Hematology	---	A decrease in neutrophils and leukocytes was noted but it was due to relatively higher than baseline values in the control groups			
Blood Chemistry	--	↓TP (F)	---	↓Gluc (M), ↓TP (F)	↓Gluc (F), ↓TP (F)
Urinalysis	---	↓Na excretion (F)	↓Na excretion (F)	↓Na excretion (F)	↓Na excretion (F)
Necropsy	---	Congestion in lungs/ dead animal	---	---	---
Organ Weight	---	↓ liver (F)	↓ heart (F)	↓ heart (F)	↑ kidney (F)
Histology	---	Congestion and edema of lungs/dead animal	---	---	---

[1] --- No abnormal findings

Twenty-eight-day Oral Toxicity Study in Juvenile Rats

A suspension of ME1207 granules in sterile water was administered orally by gavage tube, to three-day-old Sprague-Dawley rats (12/sex/group) at dose levels of 0, 50, 150, or 450 mg/kg/day for 28 days. Evaluations for treatment-related effects were based on observations, body weights, food consumption, hematology, coagulation, serum chemistry, urinalysis, gross pathology, organ weights, and microscopic histopathology.

One low-dose animal died, but the death was clearly due to a dosing accident. The rate of body weight gain was decreased in the mid and high-dose groups, but food consumption was not decreased. Signs suggestive of mild anemia (decreased erythrocytes, hemoglobin, hematocrit) occurred in all treated groups.

There were decreases in prothrombin times in the mid and high-dose females, but not in males. The decreases were statistically significant, but probably not biologically significant. Serum chemistry changes such as elevated transaminases and creatine phosphokinase occurred, mainly in the high-dose group, but there were no changes in BUN or creatinine. Renal tubular degeneration, and regeneration were seen microscopically in a few animals from the high-dose group. Loose stools and cecal enlargement also occurred in the high-dose group.

Twenty-eight-day Intravenous Toxicity Study in Rats

ME1206 was dissolved in sterile water and administered intravenously to Sprague-Dawley rats (10/sex/group) at doses of either 0, 31, 125, or 500 mg/kg/day for 28 days. Evaluations for treatment-related effects were based on clinical observations, body weights, food consumption, ophthalmic examinations, hematology, coagulation, serum chemistry, urinalysis, organ weights, and gross and microscopic histopathology.

The high-dose was associated with atrophy of the renal tubular epithelium. The results are shown in the following table.

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DOSES (MG/KG/DAY)	0	31	125	500
Animals/Grp/ M/F	10/10	10/10	10/10	10/10
Deaths	0	0	0	0
Clinical Signs	---[1]	Incidence of wet feces mainly in high dose group		
Body Weight Gain	---	---	---	---
Food Consumption	---	---	---	---
Water Consumption	---	↑	↑	↑↑
Ophthalmology and Audiometry Effects	---	---	---	---
Hematology	---	---	---	---
Blood Chemistry	---	↓Ca (M)	↓ Alb & A/G (M) ↓TG, Gluc (F)	↓ TP, Alb, TG and A/G (M) ↓ TG and Gluc (F)
Urinalysis	---	---	↓ Na (F) / D16 & 27	↓ Na (F) D16 & 27
Necropsy	---	Enlarged Cecum,	Enlarged Cecum,	Enlarged Cecum, Atrophied thymus, prostate and testes in one animal – due to spontaneous hypoplasia
Organ Weights	---	---	↓liver (F)	↓liver (M, F), ↓Thymus (M), ↑ Spleen and Kidney
Histology	---	---	---	Kidney changes: renal tubular dilation, atrophy/ regeneration of tubular epith. And round cell infiltration in kidneys Animal No.34: Changes in testes, thymus, bone marrow – not related to ME1206

[1]--- No abnormal findings

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Twenty-eight-day Oral Toxicity Studies in Dogs

ME1207 was administered orally in gelatin capsules to beagle dogs once daily for 28 days. The doses were either 0 (empty capsule), 125, 250, 500, or 1000 mg/kg/day. Evaluations for treatment-related effects were based on clinical observations, body weights, food consumption, ophthalmic examinations, electrocardiography, body temperatures, hematology, coagulation, serum chemistry, urinalysis, organ weights, and gross and microscopic histopathology.

The results are shown in the following table.

DOSES (MG/KG/DAY)	0	125	250	500	1000
M/F	4/4	4/4	4/4	4/4	4/4
Deaths	0	0	0	0	0
Clinical Signs	---[1]	Compound in feces of all treated dogs on Day 1 or Day 2 of the study			
Body Weight Gain	---	---	---	---	---
Food Consumption	---	---	---	---	---
Water Consumption	---	---	---	---	---
Urine Volume	---	---	---	---	---
Ophthalmology Audiometry ECG Body Temperature	--- --- --- ---	--- --- --- ---	--- --- --- ---	--- --- --- ---	--- --- --- ---
Hematology	---	---	---	---	---
Blood Chemistry	---	↓ α_2-globulin	↓ α_2-globulin	↑ BUN, cholesterol and ChE; ↓ gamma globulin (F), ↓ α_2-globulin	↑ BUN, cholesterol and ChE; ↓ gamma globulin (F), ↓ α_2-globulin
Urinalysis	---	---	---	---	---
Renal Function	---	---	---	---	---
Necropsy	---	---	---	---	---
Organ Weight	---	↓ pituitary (F)	---	---	---
Histology	---	---	---	---	Slight glomerular atrophy of kidney (1 F)

[1] --- No abnormal findings

Note that particles of drug were observed in dog feces, indicating that the animals had not been systemically exposed to the entire dose.

Twenty-eight-day Oral Toxicity Study in Juvenile Dogs

Gelatin capsules containing ME1207 granules were administered orally, to beagle puppies, 3-4 weeks of age (3/sex/group) at dose levels of 0, 50, 150, or 450 mg/kg/day for 28 days. Evaluations for treatment-related effects were based on observations, body weights, food consumption, hematology, coagulation, serum chemistry, urinalysis, electrocardiograms, body temperatures, ophthalmologic examination, hearing examinations, gross pathology, organ weights, and microscopic histopathology.

There were no deaths in the study. Mucous and watery feces, and bloody feces were observed sporadically. A single instance of drug in the feces was observed in two high-dose dogs. Statistically significant decreases in erythrocytes and leucocytes occurred, but because of variation in the control group, it was not possible to determine if the differences were treatment-related. At necropsy, a ~~hemocyst in the right~~ atrioventricular valve was observed in six treated animals (three low-dose, two mid-dose, one high-dose). The finding was not seen in any control animals. Microscopically, the hemocysts were described as telangiectasis, and were interpreted as possibly congenital.

Twenty-eight-day Intravenous Toxicity Study in Dogs

ME1206 was dissolved in water for injection and administered intravenously to beagle dogs (3/sex/group) at doses of either 0, 125, 250, or 500 mg/kg/day for four weeks. Evaluations for treatment-related effects were based on observations, food consumption, water consumption, body weights, body temperatures, electrocardiograms, ophthalmic examinations, auditory examinations, hematology, coagulation, serum chemistry, urinalysis, organ weights, and gross and microscopic histopathology.

No deaths occurred in the study. Occasional episodes of vomiting occurred in most animals in the high-dose group. One animal in this group had a transient decrease in food consumption, water consumption, and body weight. A corneal opacity was observed in the right eye of one high-dose animal. Treatment-related increases in serum transaminases occurred in the high-dose females, but not in the males. No treatment-related toxicity was seen in the low and mid-dose animals.

Six-month Multiple-dose Studies

Six-month studies were conducted in rats and dogs, using both the bulk powder and the granule formulation. The six-month studies are considered to represent a more definitive description of the chronic toxicity of the antibiotic (as compared to the four-week studies).

Six-Month Oral Toxicity Studies in Rats

In two studies, ME1207 was administered orally (by gavage) to rats once daily for a period of six months. The doses were 0, 31, 63, 125, 250, or 500 mg/kg/day of the bulk powder and 0, 62.5, 125, 250, 500, or 1000 mg/kg/day of the granules. The rats were four weeks old at the start of dosing. There were 20 males and 20 females at each dose level, with 12 extra animals (6 male, 6 female) in the control and high-dose groups; the extra animals were used for a recovery phase. Evaluations for treatment-related effects were based on clinical observations, body weights, food consumption, ophthalmic examinations, hematology, coagulation, serum chemistry, urinalysis, organ weights, gross and microscopic histopathology (and audiometry in the range-finding study).

The following is a list of the tissues examined by light microscopy: cerebrum, cerebellum, heart, lungs, bronchus, liver, kidneys, pituitary, thymus, adrenals, spleen, pancreas, testes, epididymides, prostate, seminal vesicle, ovaries, uterus, vagina, thyroid gland (with parathyroid), salivary glands (parotid, sublingual, submandibular), stomach, duodenum, jejunum, ileum, cecum, colon, rectum, femur (with bone marrow), sternum, spinal cord, mesenteric lymph nodes, submandibular lymph nodes, tongue, esophagus, trachea, mammary glands, Harderian glands, urinary bladder, skin, aorta, skeletal muscle, larynx, and eyes.

Liver and kidneys were also examined by electron microscopy.

There was no treatment-related mortality in this study; four animals died as a result of gavage accidents.

Slight, but statistically significant decreases in red blood cells, hemoglobin, and hematocrit occurred in high-dose females, but not in males, or in any other dose group. White blood cells and platelets were not affected.

The serum chemistry changes (statistically significant) that occurred in both sexes were decreases in glucose, total protein, creatinine, and chloride, along with increases in inorganic phosphorus, and the albumin/globulin ratio. In males, there were statistically significant increases in alkaline phosphatase, ALT, and AST, but in females alkaline phosphatase was unchanged, and ALT, and AST were decreased, although the decreases were not statistically significant.

Cecal enlargement was observed microscopically in most animals from the 500 and 1000 mg/kg/day groups.

A number of other effects such as changes in food consumption, body weights, organ weights, and microscopic findings were seen in this study, but some of these findings may be incidental and not necessarily treatment-related. The findings from the granule study are summarized in the following table (fewer effects were seen in the bulk powder study at the lower doses).

DOSES	0	62.5	125	250	500	1000

(mg/kg/day)						
Animals/M/F	20/20[1]	20/20	20/20	20/20	1M[2],2F[3]	20/20[1]
Deaths	0	0	0	0	1M[2],2F[3]	1M[3]
Clinical Signs	-----[4]	Dose dependent defecation in all male dosage groups. Defecation observed in females in the two top dose groups.				
				Salivation observed in male rats at 250 mg/kg or more and in female rats at 1000 mg/kg.		
		------				Soft stools (M)
Body Weight	----	------				↓ (M), ↓(F)
Food Consmp.	----		↑(F)	↑ (M)	↑ (M), ↑(F)	↑ (M)
Ophthalmology	----	-------				
Urinalysis	----	↓ pH				
		↓ Na (M, F)	↓ Na (M, F)	↓ Na (M,F)	↓ Na (M, F)	↓Na (F)
		------				↑ Specific gravity
Hematology	----	-----			↑ MCV (M)	↑ MCV (M), ↓ RBC (M*,F), ↓ HCT (F), ↓ Hb (F)
Blood Chemistry	----	↓ Creatinine (F)	↓ Total protein (M), ↑ A/G ratio (M), ↓ Cl (F)	↓ Creatinine (F), ↓Cl, ↓ T prot. (M), ↑ A/G ratio (M)	↓ Creatinine (M,F), ↓ Glucose (M,F), ↓ Total protein (M),↑ A/G ratio (M), ↓ Cl (F), ↑ IP (F)	↓ Creatinine (M,F), ↓ Glucose (M,F), ↓ Total protein (M,F), ↓ Cl (M,F), ↑ A/G ratio (M,F), ↑ IP (M,F)
	------				↑ AST, ALT and ALP (M)	
Organ Weight: Absolute	-----			↑Kidney (M,F), ↑*liver (F)	↑Kidney(M,F), ↑ liver (F), ↑ thyroid (F)	↑Kidney(F),↑adrenal(F), ↑uterus(F),↑*liver(F)
Relative	-----		↑Kidney (F), ↑Liver (F)	↑Kidney (M,F) ↑ liver(F)	↑Kidney(M,F), ↑ liver (F), ↑ spleen (M), ↑ Heart (F)	↑Kidney(M,F),↑adrenal(M,F), ↑uterus(F), ↑liver (F), ↑ brain (M,F), spleen(M,F), heart (M,F), ↑epididymes, ↑ pituitary (F)
Necropsy	-------				Cecum enlargement	
Histology	-----	Focal myocarditis			-----	Focal myocarditis
	------				Liver: focal necrosis (1M)	-----
	------			Glandular stomach: edema of submucosal layer		

[1]6 males and 6 females were added to vehicle control group and 1000 mg/kg group as recovery group animals
[2]Moribund killed on Day 29, moribund status was attributed to a gavage error
[3]Death was attributed to a gavage error
[4] ----- No abnormal findings
*Not statistically significant

Six-Month Oral Toxicity Studies in Dogs

In two studies, ME1207 was administered orally (in capsules) to dogs once daily for a period of six months. The doses were 0, 125, 250, 500, or 1000 mg/kg/day of the bulk powder, and 0, 90, 150, or 250 mg/kg/day of the granules. The dogs were five to seven months old at the start of dosing, and there were four males and four females at each dose level. Evaluations for treatment-related effects were based on clinical observations, body weights, food consumption, water consumption, body temperatures, ophthalmic examinations, audiometry, electrocardiography, hematology, coagulation, serum chemistry, urinalysis, organ weights, and gross and microscopic histopathology.

The following is a list of the tissues examined by light microscopy: brain, heart, lungs, bronchus, liver, kidneys, pituitary, thymus, adrenals, spleen, pancreas, testes, prostate, ovaries, uterus, vagina, thyroid gland (with parathyroid), salivary glands (submandibular), stomach, duodenum, jejunum, ileum, cecum, colon, femur, bone marrow, sternum, spinal cord, mesenteric lymph nodes, submandibular lymph nodes, tongue, esophagus, trachea, mammary glands, urinary bladder, skin, skeletal muscle, and eyes.

Liver and kidneys were also examined by electron microscopy.

There were no deaths in either study. Diarrhea and soft stools occurred in the 500 and 1000 mg/kg/day groups, and these effects were attributed to the pharmacological effects on the antibiotic on the intestinal flora. In some cases, particles of drug were observed in the feces, indicating that the dogs had not been systemically exposed to the entire dose.

Hematological parameters were not affected. There were statistically significant increases in ALT, AST, and cholesterol in both sexes as shown in the following table. There were no increases in creatinine; there were scattered (occasionally statistically significant) increases in BUN values. At necropsy, liver and kidney weights (relative) were increased. Microscopically, vacuolation, fibrosis, and hyaline droplets in the cytoplasm were seen in hepatocytes from animals (both sexes) dosed with 250 mg/kg/day and higher. No microscopic changes were seen in the kidney. The findings from the bulk powder study are summarized in the following table (fewer effects were seen in the granule study at the lower doses).

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DOSES (mg/kg/day)	0[1]	125	250	500	1000
Animals/M/F	4/4	4/4	4/4	4/4	4/4
Deaths	0	0	0	0	0
Clinical signs	------[2]			Soft stools or diarrhea (1M)	Soft stools or diarrhea (2F)
Body weight	-----			↓ (≥ Day 140)	-----
Food consumption	-----				
Water consumption	-----				
Urine volume	-----				
Body temperature	-----				
Audiometry	-----				
Ophthalmology	-----				
Electrocardiogram	-----				
Hematology	-----				
Blood chemistry	-----		↑ALT (M) ↑ALP (M) ↑cholesterol (F)	↑ALT (F) ↑AST (F) ↑ALP (M) ↑CPK(F) ↑cholesterol(F)	↑ALT (M,F), ↑AST (M,F) ↑HBD (M), ↑LDH (M), ↑ALP (M, F), ↑ChE (M), ↑CPK (M), ↑cholesterol (M, F)
Urinalysis	-----			↓ Sodium (M,F), ↓ total sodium (M,F)	
Organ weight	-----				Absolute: ↑*Kidney (M) Relative: ↑ Kidney (M)
	------			Relative: ↑ Liver (F),	Relative: ↑* Liver (F)
Necropsy	-----				
Histology	-----		Liver: mild cell infiltration, vacuolation, fibrosis or hyaline droplets in the cytoplasm (M,F)		

[1]Animals given empty capsules
[2] ----- No abnormal findings
*Not statistically significant

Reproductive Studies

In the reproductive studies, the compound was administered orally by gavage, in a suspension of 0.1% carboxymethylcellulose (unless noted otherwise).

Fertility and Reproduction Study (with Teratology) in Rats

ME1207 bulk drug powder was administered orally to male and female rats in a 0.1% carboxymethylcellulose suspension at doses of 0 (vehicle), 125, 250, 500 or 1000 mg/kg/day. Males received the drug for 63 days before mating and throughout the mating period. Females received the drug for 14 days before mating, throughout the mating period, and for the first 7 days of pregnancy. On gestation day 20, maternal animals were sacrificed and fetuses were removed for morphological examination. Approximately one-third of the fetuses obtained from each dam, were fixed in Bouin's fluid for visceral examination, while the other two-thirds were stained with alizarin red for skeletal examination.

There were no treatment-related effects on the numbers of corpora lutea, pregnancy rate, percentage of implantations, resorptions, live and dead fetuses, sex ratio, fetal weights, or fetal abnormalities. The study results are presented in the following table:

DOSES (mg/kg/day)	0	125	250	500	1000
# Animals (M/F)	25/25	25/25	24/24	25/25	25/25
Treated males					
Deaths	0	0	1M(misdose)	0	0
Clinical signs	---[1]	Loose stool	Loose stool	Loose stool	Loose stool
Body weight gain	---	↓	↓	↓	↓
Food consumption	---	↑ or ↓	↑ or ↓	↑ or ↓	↑ or ↓
Water consumption	---	↑	↑	↑	↑
Copulation rate (%)	100	100	100	100	100
Necropsy findings	---	Swollen cecum	Swollen cecum	Swollen cecum	Swollen cecum
Testes weights[2]	3.17	3.22	3.17	3.22	3.20
Treated females					
Deaths	0	0	0	0	0
Clinical signs	---	Loose stool before pregnancy	Loose stool before & during pregnancy	Loose stool before & during pregnancy, alopecia	Loose stool before & during pregnancy, alopecia
Body weight gain	---	---	---	---	↓during pregnancy
Food consumption	---	↑ or ↓	↑ or ↓	↑ or ↓	↑ or ↓
Estrus[2] (per week)	1.7	1.9	1.8	1.5	1.6
Copulation rate (%)	100	100	100	100	100
Pregnancy rate (%)	84.0	72.0	91.7	72.0	92.0
# Corpora lutea[2]	16.6	15.7	15.5	14.4	14.3
# Implantations[2]	13.9	14.6	14.6	13.7	13.6
Implantation (%)	84.3	93.8	93.8	95.4	94.7
Necropsy findings	---	Swollen cecum	Swollen cecum	Swollen cecum	Swollen cecum
Fetuses:					
Implantation (%)[2]	84.3	93.8	93.8	95.4	94.7
Postimplant. loss(%)[2]	7.4	3.6	5.7	6.8	4.8
Resorption (%)[2]	7.4	3.6	5.7	6.8	4.8
Fetal Deaths (%)[2]	0	0	0.3 (one)	0	0
No.of live fetuses[2]	12.9	14.1	13.7	12.7	13.0
Live fetuses (%)[2]	92.6	96.4	94.3	93.2	95.2
Body weights (M/F)[2]	3.3/3.2	3.4/3.2	3.5/3.3	3.7/3.5	3.5/3.3
Sex ratio	0.88	1.06	0.96	0.89	1.03
Malformations (%)					
External	---[1]	---	---	---	---
Visceral	---	---	---	---	---
Skeletal	---	---	---	---	---

[1] No abnormal finding
[2] Mean values

Teratology Study (with Postnatal Development) in Rats

ME1207 bulk drug powder was administered orally in a 0.1% carboxymethylcellulose suspension to female rats from days 7 to 17 of pregnancy at 0 (vehicle), 125, 250, 500, or 1000 mg/kg/day. Each group consisted of 38 to 41 pregnant females. On gestation day 20, approximately two-thirds of the pregnant rats in each dose group were subjected to Cesarean section and the remaining females were allowed to deliver their litters spontaneously for the nursing study. Four days after birth, the litters were culled with some pups (4M and 4F/each litter) selected randomly for developmental observations and behavioral testing and other pups (10 /sex/group separated from mother on day 21 after birth) for mating at 10 weeks of age. The remaining pups were necropsied.

Offspring from the groups dosed at 250 mg/kg/day and higher had wavy ribs, and reduced ossification of the sacrococcygeal vertebrae. At 500 mg/kg/day and higher the numbers of sacrococcygeal vertebrae were decreased. Heart weights were decreased in male offspring (but not females) from the groups dosed at 250 mg/kg/day and higher. The study results are presented in the following table:

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DOSES (MG/KG/DAY)	0	125	250	500	1000
Results for Dams/Fetuses -- Cesarean Section					
Number of Dams	27	29	26	29	26
Mean # Corpora Lutea [2]	16.3	15.6	15.4	15.4	14.9
Mean # Implantations [2]	15.2	14.1	14.3	14.4	14.0
Implantation Index (%)	93.5	90.9	92.9	94.0	94.1
Body Wts - M/F fetuses [2]	3.8/3.6	3.8/3.6	3.7/3.5	3.6/3.5	3.8/3.5
Number of live fetuses [2]	14.3	13.1	13.5	13.9	13.6
Sex Ratio	1.02	1.07	0.98	0.86	0.86
Postimplantation Loss(%) [2]	6.2	6.6	5.7	4.4	2.9
Malformations (%) Visceral:	---	---	---	---	---
Skeletal:					
Wavy rib (%)	0	0	3.7	0	2.7
# Sacrococcygeal vertebrae (ossification)	5.7	5.7	5.6	5.4 (Reduced)	5.4 (Reduced)
Combined anomalies (%)	0.4	0	1.2	0.7	1.3
Results of Data F0 Dams --Spontaneous Delivery					
No. pregnant/ delivered Spontaneously	12/12	12/12	12/12	12/12	13/13
Gestation Period (days) [2]	21.7	21.8	21.9	21.7	21.8
No. of Implantations [2]	14.8	14.8	14.8	14.8	14.7
Necropsy after weaning	---	Uterine edema (hydrocele) in 2-3 dams; Swollen cecum		Thumb size SC tumor	Swollen cecum
F1 Pup data -- Spontaneous Delivery					
No of offspring at birth [2]	13.8	13.8	14.2	13.9	13.7
No. of survivors at birth [2]	13.4	13.6	13.8	13.8	13.5
No. of survivors at day 4 [2]	13.4	13.3	13.8	12.9	13.3
Sex ratio (male/female)	0.71	0.93	0.88	0.68	1.08
Physical development	---	---	---	---	---
Behavioral development	---	---	---	---	---
Malformations	---	---	---	---	---
Developmental Indices	---	---	---	---	---
Open Field Test	---	---	---	---	---
Shuttle Box Test	---	---	---	---	---
Water Maze Test	---	---	---	---	---
Organ Weights (8 weeks old)	---	---	Reduced absolute and relative weights of heart Males only		
F1 Dams: Mating (%)	100	100	100	100	100
Pregnancy Rate(%)	80	100	100	100	80
# Corpora Lutea [2]	15.5	14.4	15.3	15.9	14.1
# Implantations [2]	14.3	13.3	15.1	14.9	12.6
Implantation Rate (%)	91.1	90.3	98.7	93.0	88.3
Post-Implantation Loss (%)	6.2	7.3	3.0	4.4	3.4
F2 # Live Fetuses (Day 13) [2]	13.4	12.6	14.6	14.2	12.1

[1] No abnormal finding [2] Mean values;

Perinatal and Postnatal Toxicity Study in Rats

ME1207 in 0.1% carboxymethylcellulose was administered orally by gavage to pregnant rats at 0 (vehicle control), 90, 250 or 750 mg/kg/day from day 17 of gestation, and until postpartum day 20. Females were allowed to deliver their litters spontaneously and to nurse until postpartum day 21. Newborn pups were culled to 8/dam where possible, maintaining the sex ratio. The offspring were subjected to a standard battery of tests to evaluate behavior, development, and reproductive ability. The pups were monitored for normal development, including developmental parameters (separation of auricles, eruption of upper incisors, emergence of abdominal hair, opening of eyes) and function tests (pivoting, righting reflex, traction test, pain response, flexor response, visual placing response, auditory reflex, pupillary reflex). After weaning, all pups were sacrificed except 2/sex/group, which were used for reproductive ability and behavior/learning tests. These latter animals were observed daily for clinical signs, testes descent, and vaginal opening. After copulation (approximately week 10), males were sacrificed immediately while females were sacrificed on day 13 of pregnancy.

No developmental or reproductive abnormalities occurred in this study. The results are summarized in the following table.

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ON ORIGINAL

DOSES (mg/kg/day)	0	90	250	750
# Animals	24	24	24	23
Dams (F0)				
Deaths	0	0	1 (misdose)	0
Clinical signs	---[1]	Occasional loose stool from pregnancy D21 to weaning day		
Body weight gain	---	---	↑ During nursing period	
Food consumption	---	↓ During gestation (Day 18-21) in all groups. ↑ During lactation		
Water consumption	---	↑ During pregnancy and lactation in all groups		
Pregnancy period (days)	22.1	22.0	22.1	22.2
# Implantations[2]	15.3	15.3	15.3	15.4
Necropsy findings	---	---	swollen cecum	-
Organ weights	---	↑Adrenal	↑Adrenal and kidney	
F1 Newborns				
Live—Postnatal Day 0	345	335	337	330
Postnatal Day 4	344	329	321	323
Postnatal Day 4 M : F Ratio	97:95	94:94	95:89	93:89
Weaning Date M : F Ratio	96:94	93:94	94:88	93:89
Body Weight (M/F)	---	↓ On postnatal Days 21 and 28 (M) and 14-28 (F); ↑ on postnatal Day 70 (M)	↑ On postnatal Days 49-70 (M)	↑ On postnatal Day 70 (M)
Malformations	---	---	--	---
Developmental Indices	---	---	---	---
Open Field Test	---	---	---	---
Water Maze Test	---	---	---	---
Necropsy—3 weeks old	---	---	---	---
Necropsy--8 weeks old	---	---	---	---
Organ weights—3 weeks	---	---	---	---
Organ weights--8 weeks	---	---	---	---
Mating Rate (%)	87.5	100	91.3	91.3
Pregnancy Rate (%)	95.2	95.8	95.2	81.0
# Corpora Lutea[2]	14.7	15.1	15.1	15.0
# Implantations[2]	14.2	14.3	14.8	14.5
F2 Fetuses				
Implantation Rate (%)	96.6	94.5	98.1	96.5
Post-Implantation Loss (%)	5.4	5.5	5.1	2.2
# Live Fetuses (Day 13)	13.4	13.5	14.0	14.2

[1] No abnormal finding
[2] Mean values

Teratology Studies in Rabbits

ME1207 bulk drug powder was administered orally to female rabbits as a 0.1% carboxymethylcellulose suspension on days 6 to 18 of pregnancy at doses of 0 (vehicle control), 2, or 4 mg/kg/day in one study, and at doses of 0, 7.5, 15, or 30 mg/kg/day in a second study. Dams were monitored during pregnancy and were subjected to Cesarean section on day 29 of pregnancy.

In another study, a mixture of ME1207 granules and citric acid granules (tablet formulation) dissolved in water, was administered orally by gavage to groups of pregnant rabbits (14/group) at dose levels corresponding to 0, 10, 30, or 90 mg/kg/day during gestation days 6-18. On day 29 of gestation, the dams were sacrificed, and the ovaries and uterus were removed. The numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. About one-third of the fetuses were prepared for examination of visceral organs (Bouin solution), and the other two-thirds were prepared for skeletal examination (alizarin red).

Abortion occurred in one animal each at 7.5 and 15 mg/kg/day and in seven animals at 30 mg/kg/day. In addition, one animal at 30 mg/kg/day delivered prematurely. There was a significant reduction in the number of live fetuses in all ME1207-treated groups when compared with controls. A forelimb deformity was seen in one fetus from the 30 mg/kg/day dose group, but no other external, visceral, or skeletal abnormalities were found.

In the high-dose group from the granule study, ten dams aborted fetuses, and one dam was found dead. Abortion was observed in three dams from the 30 mg/kg group. No abortions occurred in the low dose group. The incidence of resorptions and dead fetuses was significantly increased in the high-dose group. A number of minor skeletal and visceral anomalies occurred in both control and treated animals, but did not appear to be treatment-related.

No treatment-related teratogenic effects were observed in another exploratory study in which rabbits were dosed at either 30 or 60 mg/kg/day during gestation days 6-9, or during gestation days 10-14, which are the critical periods for limb development.

The findings from the powder and granule studies are shown in the following two tables:

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ON ORIGINAL

DOSES (MG/KG/DAY)	0	7.5	15	30
Dams/Group	16	18	16	17
Deaths	0	0	0	0
Abortion/Premature Birth	0/0	1/0	1/0	7**/1
Clinical Signs	---[1]	Dose-dependent reduction in feces; loose stool		
Food Consumption	---	↓ at early stage of treatment; ↑ at later stage of pregnancy		↓ from early stage of treatment to pregnancy D22
Water Consumption	---	↓ During treatment with tendency to recover		↓ from Day 8 until sacrifice
Body Weight Gain	---	Mild suppression	Suppressed	Suppressed
Necropsy	---	---	---	Swollen cecum in animals that aborted
# Corpora Lutea[2]	10.4	10.9	10.1	10.1
# Implantations[2]	10.0	8.9	8.8	8.8
# Live Fetuses[2]	9.3	7.2*	7.5*	6.2**
Post-Implantation Loss(%)[2] (Resorptions+ deaths)	6.99	16.57	13.09	26.00
Fetal Weight(G)[2]. (M/F)	43.92/44.5	45.97/45.38	46.74/45.75	43.39/38.03**
Sex Ratio	1.18	1.12	0.9	0.75
Malformations[3]				
External	---	---	---	---
Visceral	---	---	---	---
Skeletal	---	---	---	---

* $p < 0.05$, ** $p < 0.01$

[1] No abnormal finding

[2]Mean values

[3]Changes considered within historical control values or not clearly treatment-related are not listed.

APPEARS THIS WAY
ON ORIGINAL

DOSES (MG/KG/DAY)	0	10	30	90
Dams/Group	12	14	14	14
Deaths	0	0	0	1
Clinical Signs Abortions	0	0	3	10
Food Consumption	---[1]	---	↓	↓↓
Body Weight Gain	---	---	↓	↓↓
Necropsy	Kidney discoloration (1F)	Kidney discoloration(2F) Fatty Liver (1F)	Cecal distension (3F) Fatty Liver	Cecal distension (12 F) Fatty Liver
Organ Weight	----	----	----	----
# Corpora Lutea[2]	10.8	9.3	10.9	10.6
# Implantations[2]	9.0	7.6	9.1	9.4
# Live Fetuses[2] (%)	90.77	75.46	74.71	45.20 *
Post-Implant Loss[2] Early and Late Resorptions (%)	3.98	18.85	10.07	51.47 *
Dead Fetuses[2] (%)	5.25	5.69	15.22	3.33
Fetal Weight(M/F)[2]	----	---	---	↓
Sex Ratio	----	----	----	----
Malformations External	----	----	----	----
Visceral	----	----	----	----
Skeletal	----	----	----	----

[1]No abnormal finding * $p<0.05$

[2]Mean values

Genetic Studies

The genetic toxicology studies were conducted using standard methodology. Appropriate positive and negative controls were carried through the assays, in order to validate the integrity of the experiments. A metabolic activation system (S-9) was used in most of the studies, to detect indirect acting mutagens. The S-9 was a post-mitochondrial supernate obtained from the livers of rats that had been induced with phenobarbital and 5,6-benzoflavone.

Cefditoren and cefditoren pivoxil were tested for clastogenic potential in a fibroblast cell line, derived from Chinese hamster lung. Cefditoren pivoxil was tested at concentrations of up to 300 mcg/ml in the absence of metabolic activation, and at concentrations of up to 800 mcg/ml with metabolic activation.

Cefditoren pivoxil, both with and without metabolic activation, induced a significant increase in the incidence of cells with chromosomal aberrations (chromatid gaps, breaks, and exchanges). Cefditoren did not induce chromosome aberrations in this assay, either with or without metabolic activation.

The metabolites of cefditoren pivoxil were studied in this assay to determine which component might be responsible for the clastogenicity. Pivalic acid had no effect in this assay. However, the incidence of cells with chromosome abnormalities was significantly increased by formaldehyde, when tested without metabolic activation, but not when tested with metabolic activation. It was concluded that the clastogenic effect seen with cefditoren pivoxil was due to the in vitro generation of formaldehyde. It was also concluded that if generated in vivo, formaldehyde would be metabolically inactivated, and would not be clastogenic.

Neither cefditoren or cefditoren pivoxil produced chromosomal aberrations when tested in an in vitro human peripheral blood lymphocyte assay. ME1207 was incubated with lymphocytes at concentrations up to 100 µg/mL without metabolic activation and up to 800 µg/mL with metabolic activation. ME1206 was incubated at up to 1600 µg/mL in both systems.

Both compounds were also non-clastogenic when tested in the in vivo mouse micronucleus assay. ME1207 was suspended in 0.1% carboxymethylcellulose and administered orally by gavage mice as a single dose at 1250, 2500 or 5000 mg/kg. ME1206 was administered intravenously at doses of 250, 500, and 1000 mg/kg. The frequency of micronucleated bone marrow polychromatic erythrocytes from treated mice was similar to those from the solvent control animals.

Cefditoren, cefditoren pivoxil, and ME1207-NRS were all non-mutagenic when tested (with or without metabolic activation) in the bacterial reverse mutation (Ames) assay using five strains of *S. typhimurium* (TA98, TA100, TA1535, TA1537, and TA1538) and one strain of *E. coli* (WP2uvrA). The compounds were dissolved in dimethyl sulfoxide (DMSO) and tested at concentrations up to 10 µg/plate for ME1206, 300 µg/plate for ME1207, and 400 µg/plate for ME1207-NRS. Higher concentrations resulted in inhibition of bacterial cell growth.

Cefditoren pivoxil was not mutagenic in the mouse lymphoma assay, with or without metabolic activation (HGPRT locus in cultured L5178Y cells). The compound was dissolved in DMSO and tested at concentrations of up to 150 mcg/ml without metabolic activation, and 250 mcg/ml with metabolic activation. Two positive controls (benzopyrene and ICR-191) did increase mutation frequency as expected.

Cefditoren pivoxil, at concentrations of 1, 3, 10, and 30 mcg/ml, did not induce in vitro cell transformation in a fibroblast cell line derived from mouse fetus (BALB/3T3).

An ex vivo study was conducted to evaluate the effects on unscheduled and replicative DNA synthesis. Cefditoren pivoxil was suspended in 0.1% carboxymethylcellulose, and administered orally to rats as a single dose of either 100, 300, or 1000 mg/kg. The animals were sacrificed 80 minutes after dosing. Strips of gastric mucosa were harvested and incubated, and the incorporation of tritiated thymidine was measured. Cefditoren pivoxil did not result in increased unscheduled or replicative DNA synthesis.

Special Studies

The effects of cefditoren pivoxil and a marketed comparator drug (cefteram pivoxil) on carnitine levels were studied in juvenile dogs. Eighteen beagle puppies, 3-4 weeks or age, were divided into six groups of three animals each. Dogs of both genders were used, but the exact numbers of each sex were not reported. The groups received the following treatments:

Group 1 empty gelatin capsules
Group 2 cefditoren pivoxil 150 mg/kg
Group 3 cefteram pivoxil 150 mg/kg
Group 4 empty gelatin capsules
Group 5 cefditoren pivoxil 150 mg/kg
Group 6 cefteram pivoxil 150 mg/kg

Each group was dosed once daily for 28 days. Groups 1, 2, and 3 were sacrificed after 28 days of dosing, while groups 4, 5, and 6 were placed on a treatment-free recovery period for an additional 28 days, and then sacrificed. At necropsy, plasma, cardiac muscle, and skeletal (thigh) muscle were collected.

Both treatments reduced total plasma carnitine, but the levels had returned to near normal, after 28 days of recovery as shown below:

	Total plasma carnitine (nmoles/ml)	
	After dosing	After recovery
Group 4	21.8	20.3
Group 5	11.6	19.9
Group 6	10.9	18.2

There were corresponding increases in urinary carnitine as shown below:

	Total urinary carnitine (μmoles/day)	
	After dosing	After recovery
Group 4	10.0	11.3
Group 5	31.7	11.5
Group 6	29.4	8.9

The animals in groups 1, 2, and 3 were sacrificed for measurement of carnitine levels in cardiac and skeletal muscles. After recovery, there were no differences between the control and cefditoren groups, however the pre-recovery values were not reported.

The effects of ME1207 on muscle carnitine levels were further investigated in young adult (5-6 month old) male beagle dogs. ME1207 in gelatin capsules, was administered orally at a dose of 250 mg/kg/day for 90 days. Two positive control groups received pivalic acid, either orally (42 mg/kg/day) by gavage tube, or intravenously (120 mg/kg/day). Empty gelatin capsules were administered to the negative control group. After dosing, some animals were allowed a 14 day recovery period. At necropsy, specimens of cardiac and skeletal (thigh) muscle were collected and assayed for carnitine content, while other specimens were prepared for microscopic histopathology.

Treatment with ME1207 and the positive controls, resulted in increases in urinary excretion of carnitine, and decreased levels of carnitine in plasma, and in both cardiac and skeletal muscle (approximately 50%). During the recovery phase, the decreased levels started to return towards normal. No microscopic abnormalities were found in either muscle tissue.

In a study in guinea pigs, cefditoren was shown to have little or no antigenic potential when tested in the active systemic anaphylaxis, and passive cutaneous anaphylaxis models. Groups of 3-5 female Hartley guinea pigs were sensitized with a series of either subcutaneous injections (with Freund's complete adjuvant) or oral doses (without adjuvant). After an appropriate interval, the animals were challenged with the compound. For systemic anaphylaxis, challenges were made by both the oral and intravenous routes; to test for cutaneous anaphylaxis, the compound was injected intravenously with Evans blue dye.

No systemic anaphylaxis was seen in the animals challenged orally; signs of systemic anaphylaxis (dyspnea, cyanosis) were seen in one of three animals challenged intravenously. No cutaneous anaphylaxis occurred.

ME1206, at concentrations of 20-40 mg/ml, gave a positive Coombs' reaction when incubated with type O blood from healthy human volunteers.

OVERALL SUMMARY AND EVALUATION

During absorption, cefditoren pivoxil is hydrolyzed to cefditoren with the release of pivalic acid and formaldehyde. The pivalic acid is conjugated with endogenous carnitine and excreted. This process results in decreased levels of carnitine in cardiac muscle, skeletal muscle, and plasma. In the dog study, the decreases in carnitine were shown to be reversible, and no microscopic abnormalities occurred in either muscle tissue. Lipid metabolism was not examined in these animals.

Cefditoren was shown to have a relatively low order of toxicity in animal toxicology studies. The effect seen most commonly was cecal distension in rats, which was due to the pharmacological action of the compound on the bacterial flora of the intestine. Signs suggestive of hepatic, renal, and hematological toxicity were seen in some (but not all) of the multiple-dose studies in rats and dogs, usually at doses of 250 mg/kg/day or higher. The hematological changes included small decreases in red blood cell parameters (erythrocytes, hematocrit, hemoglobin), white blood cells (neutrophils, lymphocytes), and platelets. Increases in transaminases (ALT, AST), cholesterol, blood urea nitrogen, and creatinine occurred sporadically in several studies (although in other studies, creatinine was decreased rather than increased). Low incidences of hepatic vacuolation and focal necrosis, renal tubular degeneration, and glomerular atrophy were seen microscopically.

In reproductive studies in rats, cefditoren did not affect fertility, reproduction, or development. Cefditoren was not teratogenic in rats but was associated with reduced ossification and decreased numbers of sacrococcygeal vertebrae at relatively high doses (250-1000 mg/kg). Cefditoren caused abortions in rabbits, but the effect was seen at doses that were also associated with maternal toxicity (7.5-30 mg/kg). A limb deformity was seen in one rabbit fetus, but was not considered to be treatment-related because no deformities occurred in a repeat study.

Cefitoren and cefditoren pivoxil were both non-mutagenic in the mouse lymphoma assay and the bacterial reverse mutation assay. In a chromosomal aberration assay in Chinese hamster lung cells, cefditoren did not induce chromosome aberrations, but cefditoren pivoxil produced a significant increase in chromatid gaps, breaks, and exchanges. In a subsequent study, the aberrations were shown to be due to the liberation of formaldehyde from the pivoxil ester moiety. Neither cefditoren or cefditoren pivoxil produced chromosome aberrations in the mouse micronucleus assay, or in the human blood lymphocyte assay. Cefditoren pivoxil was also negative when tested in the unscheduled DNA synthesis test, and a cell transformation assay. No carcinogenicity studies were reported in this NDA.

No effects occurred in the safety pharmacology studies to suggest that this compound would produce a large number of serious adverse side effects.

RECOMMENDATION

From the standpoint of Pharmacology/Toxicology, approval of this NDA is recommended because of the overall safety profile associated with the compound. Although no consistent patterns of toxic effects were seen across all studies, in those studies in which a no-observable-adverse-effect level was determined, the level was most commonly estimated to be 125 mg/kg/day (750 mg/m^2 in rats, 2500 mg/m^2 in dogs).

The recommended clinical dose of 200 mg twice daily for ten days corresponds to daily doses of approximately 8 mg/kg, or about 300 milligrams per square meter of body surface. Even if the human dose is doubled to 400 mg twice daily (600 mg/m^2), there remains an adequate margin of safety (1.25 to 4 fold) between the clinical dose, and the doses that were toxic in animals.

Statements in the sections of the label that come under the purview of Pharmacology/Toxicology (Carcinogenesis, Pregnancy, Nursing Mothers, Overdosage, etc.) are supported by the data.

Comparisons between the doses used in animal studies, and the suggested human dose, are presented in both mg/kg, and in milligrams per square meter. Pregnancy Category B is correctly indicated, and the label is in an appropriate format.

The following changes to the sponsor's proposed wording for the **Carcinogenesis, Mutagenesis, Impairment of Fertility** section are suggested.

(Note: this paragraph has been rewritten in order to expand the description of the chromosomal aberration findings.)

No long-term animal carcinogenicity studies have been conducted with cefditoren pivoxil. Cefditoren pivoxil was not mutagenic in the Ames bacterial reverse mutation assay, or in the mouse lymphoma mutation assay at the hypoxanthine-guanine phosphoribosyltransferase locus. In the Chinese hamster lung, [redacted] chromosomal aberrations were produced by cefditoren pivoxil, but not by cefditoren. Subsequent studies showed that the chromosome aberrations were due to the release of formaldehyde from the pivoxil ester moiety in the in vitro assay system. Neither cefditoren or cefditoren pivoxil produced chromosomal aberrations when tested in an in vitro human peripheral blood lymphocyte assay, or in the in vivo mouse micronucleus assay. Cefditoren pivoxil was negative in the Unscheduled DNA Synthesis test. Cefditoren pivoxil [redacted]

The next sentence under **Carcinogenesis, Mutagenesis, Impairment of Fertility** should be reworded to change the number 152 to 150, and should read as follows:

In rats, fertility and reproduction were not affected by cefditoren pivoxil at oral doses up to 1000 mg/kg/day, approximately [redacted] human dose of 200 mg BID based on mg/kg/day [redacted]

The second sentence under **Pregnancy** should be reworded to change the number 152 to 150, and should read as follows:

In rats, this dose was 1000 mg/kg/day, which is approximately [redacted] human dose of 200 mg BID based on mg/kg/day [redacted]

The last three sentences under **Pregnancy** which now read:

[redacted]

should be reworded to the following:

"In a postnatal development study in rats, cefditoren pivoxil produced no adverse effects on postnatal survival, physical and behavioral development, learning abilities, and reproductive capability at sexual maturity when tested at doses of up to 750 mg/kg/day, the highest dose

tested. This is approximately [redacted] human dose of 200 mg BID based on mg/kg/day [redacted]

The **Nursing Mothers** section should be changed to read as follows: Cefditoren was [redacted] in the milk of lactating rats, [redacted] Because many drugs are excreted in human milk, caution should be exercised when cefditoren pivoxil is administered to nursing women.

[redacted]

Other than the changes described above, the draft label proposed by the sponsor, is considered acceptable as written.

Kenneth Seethaler, R.Ph., Ph.D., D.A.B.T.
Pharmacologist/Toxicologist HFD-520

cc: Original NDA 21-222
HFD-104
HFD-340
HFD-520
HFD-520/Pharm/K.Seethaler
HFD-520/MO/J.Alexander
HFD-520/Micro/J.Unowsky
HFD-520/Chem/B.Shetty
HFD-520/PM/R.Hills
HFD-520/Biopharm/F.Pelsor
HFD-520/Biostat/D.Lin

Concurrence only:

HFD-520/TLPharm/R.Osterberg

HFD-520/DepDir/L.Gavrilovich

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA
Division of Anti-infective Drug Products, HFD-520
Addendum to Pharmacology/Toxicology Review

NDA 21-222 (000) Addendum 1

Drug: Cefditoren pivoxil (Spectracef)

Reviewer name: Kenneth Seethaler, R.Ph., Ph.D., D.A.B.T.

Date of addendum: October 25, 2000

Scientific literature reviewed: Yes (x) No ( )

Information to sponsor: Yes ( ) No (x)

Toxicology Overview

The purpose of this addendum is to re-evaluate two findings from the preclinical animal studies with regard to their potential relevance to human safety. The two findings are the cecal distention that occurred in all of the rat studies, and the hemocysts of the atrioventricular valve that occurred in the juvenile dog study.

It is known that antibiotics can alter the bacterial flora in the intestine. In rodents and especially in rabbits, alteration of the bacterial flora almost always results in cecal distention and increased fecal output. In dogs and humans, the gastrointestinal effects of antibiotics are usually diarrhea and soft stools. Therefore, cecal distention is not considered to represent an unreasonable risk for humans taking Spectracef.

A reference source (1) was consulted in order to evaluate the dog hemocyst finding. According to this source, congenital hematomas (hematocysts) on the margins of atrioventricular valves are common in animals. The cysts usually do not persist for more than a few months (1).

In this NDA, the hemocyst finding occurred only in the juvenile dog study, but not in any other dog study. Although the finding was seen only in drug-treated animals, the incidence was not dose-related. The sponsor concluded that the finding was congenital, and not related to treatment. Since hemocysts are a relatively common congenital finding, and since their incidence was not dose-related, it seems probable that the effect was not treatment-related.

Conclusion

Based on an overall assessment of all of the animal studies, it is believed that the use of Spectracef by humans will not be associated with an unacceptable level of serious adverse events.

Reference

(1) Pathology of Domestic Animals
Jubb, K.V.F., Kennedy, P.C., and Palmer, N.
Academic Press, Inc. (1985)
Third Edition, Volume 3, Page 11

/S/

Kenneth Seethaler, R.Ph., Ph.D., D.A.B.T.
Pharmacologist/Toxicologist HFD-520

cc: Original NDA 21-222
HFD-104
HFD-340
HFD-520
HFD-520/Pharm/K. Seethaler
HFD-520/MO/J. Mulinde
HFD-520/MO/J. Alexander
HFD-520/Micro/J. Unowsky
HFD-520/Chem/B. Shetty
HFD-520/CSO/R. Hills

Concurrence only:

HFD-520/R. Osterberg /S/ 10/27/00

HFD-520/L. Gavrilovich /S/ 10/30/00

Cefditoren is also known by the following codes: CDTR and ME1206.
Cefditoren pivoxil is also known by the following codes: CDTR-PI and ME1207.

This NDA consisted of 322 volumes, of which 63 contained preclinical studies. Most of the studies were conducted in Japan during the years 1985-1999, but some were also conducted at contract laboratories [redacted] The Japanese reports were translated into English for this submission.

SAFETY PHARMACOLOGY

Approximately 30 general (safety) pharmacology studies were conducted in mice, rats, guinea pigs, rabbits, cats, and dogs to determine the effects of cefditoren on the various organ systems of the body. Cefditoren, usually as the sodium salt, was used in the *in vitro* experiments, and *in vivo* when the compound was administered by the intravenous, intradermal, or ocular routes. Cefditoren pivoxil, suspended with either carboxymethylcellulose or citric acid granules, was used for oral and intraduodenal administration.

The effects of the compound on blood pressure were measured in pentobarbital-anesthetized dogs. Blood pressure was unaffected by a dose of 100 mg/kg, but higher doses resulted in dose-related decreases in mean arterial pressure. Two of four anesthetized dogs died after a dose of 1000 mg/kg.

There were no other effects in the safety pharmacology studies to suggest that cefditoren would adversely influence the other organ systems of the body. The results of the safety pharmacology studies with cefditoren are summarized in the following tables. Pivalic acid, at doses of 50, 100, and 200 mg/kg, was also tested in the mouse behavioral screen, and in the dog hemodynamics model.

Test Model	Species	Compound	Dose/Concentration	Results
Irwin Behavioral Observation	Mouse	CDTR-PI Granules	1, 2, 4 g/kg, po 0.3, 0.6, 1.2 g/kg, po	No significant effects. No significant effects.
Righting Reflex	Mouse	CDTR-PI	1, 2, 4 g/kg, po	No significant effects.
Muscle Relaxation & Coordination – Inclined plane; Rotarod; Horizontal wire	Mouse	CDTR-PI Granules	1, 2, 4 g/kg, po 0.3, 0.6, 1.2 g/kg, po	No significant effects. No significant effects.
Spontaneous Locomotor Activity	Mouse	CDTR-PI Granules	1, 2, 4 g/kg, po 0.3, 0.6, 1.2 g/kg, po	No significant effects. No significant effects.
Inhibition of Pentylenetetrazol or Bemegride-Induced Convulsions	Mouse	CDTR-PI Granules	1, 2, 4 g/kg, po 0.3, 0.6, 1.2 g/kg, po	No significant effects. No significant effects.

Test Model	Species	Compound	Dose/Concentration	Results
Tremorine Inhibition	Mouse	CDTR-PI Granules	1, 2, 4 g/kg, po 0.3, 0.6, 1.2 g/kg, po	No significant effects. No significant effects.
Potentiation of Barbiturate Anesthesia	Mouse	CDTR-PI Granules	1, 2, 4 g/kg, po 0.3, 0.6, 1.2 g/kg, po	No significant effects; however dose-dependent trend for prolongation of anesthesia noted. No significant effects.
Inhibition of Acetic acid-Induced Writhing	Mouse	CDTR-PI Granules	1, 2, 4 g/kg, po 0.3, 0.6, 1.2 g/kg, po	No significant effects. No significant effects.
Body Temperature	Rat	CDTR-PI Granules	1, 2, 4 g/kg, po 0.3, 0.6, 1.2 g/kg, po	No significant effects. No significant effects.
EEG	Cat	CDTR	0.5 g/kg, iv	No significant effects.
Monosynaptic and Polysynaptic Spinal Reflex	Rat	CDTR	0.25, 0.5 g/kg, iv	No significant effects.
Local Anesthesia Corneal Reflex Cutaneous Reflex	Guinea Pig	CDTR	2, 5, 10% by ocular instillation or intradermal injection	No significant effects.
Phrenic Nerve-Diaphragm Preparation	Rat	CDTR	10, 100, 1000 µg/mL	No significant effects on response to either nerve or muscle stimulation.
Isolated Ileum Acetylcholine-, histamine-, barium chloride-and serotonin-induced contractions	Guinea Pig	CDTR	10, 100 1000 µg/mL	No significant effects on tone of preparation. No significant effects on contractions induced by ACH, Histamine, $BaCl_2$, or 5-HT; slight, non-significant, inhibition of 5-HT contraction noted at 1000 µg/mL.
Isolated Trachea	Guinea Pig	CDTR	10, 30, 100, 300, 1000 µg/mL	No significant effects on tone at 10-100 µg/mL; dose-dependent relaxation at 300 and 1000 µg/mL, which was not significantly affected by propranolol pretreatment.
Isolated Vas Deferens Norepinephrine-induced contractions	Guinea Pig	CDTR	10, 100, 1000 µg/mL	No significant effects on tone. No significant effects on NE-induced contractions at 10 or 100 µg/mL; significant potentiation of NE-induced contractions at 1000 µg/mL.
Sympathetic Ganglia Hypogastric Nerve - Vas Deferens Preparation	Guinea Pig	CDTR	10, 100, 1000 µg/mL	No significant effect on contractions induced by pre- or post-ganglionic stimulation at 10 µg/mL; dose-dependent, significant decreases in contractions induced by pre- and post-ganglionic stimulation at 100 and 1000 µg/ml. Ratio of responses to post- vs pre-ganglionic stimulation was not affected, indicating no significant effect on the ganglia.

Test Model	Species	Compound	Dose/Concentration	Results
In situ Uterine Motility	Rat	CDTR	0.1, 0.25, 0.5 g/kg, iv	No significant effects on uterine motility in either pregnant or non-pregnant rats.
Hemodynamics	Dog	CDTR	0.1, 0.25, 0.5, 1.0 g/kg, iv (over 5 min)	No significant effects at 0.1 g/kg. Small decrease in blood pressure and reduction in end tidal CO_2 at 0.25 g/kg or higher. Increases in respiratory rate, pulmonary arterial pressure, central venous pressure at 0.5 g/kg or higher. Marked decrease in blood pressure, heart rate, femoral blood flow, and maximal left ventricular dp/dt; flattening of T wave in ECG at 1.0 g/kg. Death in 2/4 dogs at 1.0 g/kg.
Carotid Reflex and Response to Autonomic Agents	Dog	CDTR	10 mg/kg/min, iv infusion	No significant effects on blood pressure responses to carotid occlusion or administration of norepinephrine, acetylcholine, histamine, or isoproterenol. Slight suppression of increased heart rate associated with ACH (presumably of reflex origin); no effects on heart rate changes associated with carotid occlusion, NE, histamine, or isoproterenol.
Isolated Atria	Guinea Pig	CDTR	10, 100, 1000 µg/mL	No significant effects on rate or force of atrial contractions.
Intestinal Transport of Charcoal Meal	Mouse	CDTR-PI	1, 2, 4 g/kg, po	No significant effects.
		Granules	0.3, 0.6, 1.2 g/kg, po	No significant effects.
Isolated Ileum	Rabbit	CDTR	10, 100, 1000 µg/mL	No significant effects on spontaneous motility of ileum.
Gastric Secretion	Rat (pylorus ligated)	CDTR-PI	0.3, 0.6, 1.2 g/kg, id	No significant effects at 0.3 and 1.2 g/kg. Significant decrease in total acid output at 0.6 g/kg. Trends for gastric fluid volume, total acid output, acidity, and pepsin secretion to decrease.
		Granules	0.3, 0.6, 1.2 g/kg, id	No significant effects at 0.3 g/kg. Significant decreases in gastric fluid volume, total acid output, and acidity, with increase in pH, at 0.6 and 1.2 g/kg. Decrease in total pepsin output but increase in pepsin concentration at 0.6 and 1.2 g/kg.
		Placebo granule formulation (citric acid)	Equivalent to 1.2 g/kg dose of CDTR-PI	Significant decreases in gastric fluid volume, total acid output, acidity, and total pepsin output. Significant increase in pH.

Test Model	Species	Compound	Dose/Concentration	Results
Gastric Emptying of Charcoal Meal	Mouse	CDTR-PI	1, 2, 4 g/kg, po	No significant effects.
		Granules	0.3, 0.6, 1.2 g/kg, po	No significant effects; tendency for gastric emptying (increased gastric contents) to be delayed at 1.2 g/kg.
Urine and Electrolyte Excretion	Rat	CDTR-PI	37.5, 75, 150 and 300 mg/kg, po	No significant effects at 37.5 mg/kg. Significant decreases in urine volume at 75, 150 and 300 mg/kg; in total Na^+ excretion at 75 and 300 mg/kg; in total K^+ excretion at 150 and 300 mg/kg; and in total Cl^- excretion at 75 and 300 mg/kg. No significant effects on pH.
		Granules	37.5, 75, 150 mg/kg, po	No significant effects at 37.5 mg/kg. Significant decreases in total Na^+ excretion at 75 and 150 mg/kg. No significant changes in urine volume, pH, total K^+ or Cl^- excretion at 75 or 150 mg/kg.
		Granules	0.3, 0.6, 1.2 g/kg, po	Significant decrease in urine volume and pH at 0.3, 0.6 and 1.2 g/kg. Significant decreases in total Na^+ excretion at 0.6 and 1.2 g/kg. Significant decrease in total Cl^- excretion at 1.2 g/kg. No significant effect on total K^+ excretion.
Creatinine and PAH Clearance; PSP test	Rat	Granules	0.3, 0.6, 1.2 g/kg, po	No significant effects.
BSP Test	Rat	Granules	0.3, 0.6, 1.2 g/kg, po	No significant effects.
Blood Clotting - *in vitro* Clotting Time, Prothrombin Time, Activated Partial Thromboplastin Time	Rabbit	CDTR	10, 100, 1000 µg/mL	No significant effect on clotting time at 10 or 100 µg/mL. Increase in clotting time at 1000 µg/mL. No significant effects on prothrombin time or APTT.
Platelet Aggregation - ADP-, Collagen-, and Arachidonic Acid-induced	Rabbit	CDTR	10, 100, 1000 µg/mL	No significant effects.
Hemolysis of Erythrocyte in Suspension	Rabbit	CDTR	10, 100, 1000 µg/mL	No significant effects.

PHARMACOKINETICS/TOXICOKINETICS

Absorption

In mice, rats, and dogs, cefditoren pivoxil absorption was rapid, but limited, following oral administration, however absorption was slower in cynomolgus monkeys. It was shown that cefditoren pivoxil was hydrolyzed to form cefditoren either during or immediately after absorption from the gastrointestinal tract.

The pharmacokinetic parameters of cefditoren in mice, rats, dogs, and cynomolgus monkeys are shown in the following table:

Species (dose)	Drug	Route	t_{max} (h)	C_{max} (μg/mL)	AUC (μg·h/mL)	$t_{1/2}$ (h)	F (%)	f_e (%)
Mouse (10 mg/kg)	CDTR-PI	p.o.	0.50	9.78	40.2	2.40	55.6	21.6
	CDTR	i.v	n.d.	n.d.	72.3	1.19	-	n.d.
Rat (20 mg/kg)	CDTR-PI	p.o.	0.44	7.55	19.8	1.34	20.2	4.0
	CDTR	i.v.	n.d.	n.d.	97.8	0.98	-	26.4
	CDTR	p.o.	n.d.	0.43	2.1	n.d.	2.5	n.d.
Dog (20 mg/kg)	CDTR-PI	p.o.	1.06	2.34	4.63	0.76	9.5	2.7
	CDTR	i.v.	n.d.	n.d.	48.9	0.38	-	n.d.
Monkey (40 mg/kg)	CDTR-PI	p.o.	4.0	0.71	2.87	n.d.	1.4	2.4
	CDTR	i.v.	n.d.	n.d.	208.6	n.d.	-	28.7

F=percent bioavailability
fe=cumulative urinary excretion
n.d. not determined

In a study in male rats to investigate the effects of feeding, ME1207 was administered orally in doses of either 20, 40, or 100 mg/kg, to groups of fasted and fed rats. Plasma drug levels were similar in both groups, indicating that fasting did not influence absorption in rats. Another study showed that fasting had very little effect on absorption in female dogs.

Another study was conducted to determine if the presence of milk in the stomach would retard the absorption of ME1207. Eight female beagle dogs were divided into two groups of four each. In one group, ME1207 (pediatric granule formulation) was administered orally in 30 ml of water, and in the other group, it was administered in 30 ml of milk. Cmax and AUC values were measured. After a one-week washout period, the groups were switched (crossover design) and re-dosed.

The Cmax and AUC values were slightly higher when the compound was administered in milk, indicating that milk does not retard the absorption of ME1207.

Pharmacokinetic determinations were also made in juvenile rats and dogs. A suspension of ME1207 (100 mg/kg) in 0.5% carboxymethylcellulose was administered orally by gavage tube to nursing, four day old, male Sprague-Dawley rats. Four animals per timepoint were sacrificed

at 0.5, 1, 2, 4, 6, 8, and 24 hours after dosing. Blood, liver, and kidneys were collected, and assayed for drug concentration.

The following pharmacokinetic parameters were measured in these rats:

Cmax: 27.1 mcg/ml	AUC: 278 mcg x hrs/ml
Tmax: 4 hours	Half-life: 2.06 hours
Vd: 1.3 L/kg	

Concentrations in the liver peaked at two hours, with a mean concentration of 5.7 mcg/g. The kidney concentrations also peaked at two hours, reaching 10.6 mcg/g.

In the juvenile dog study, two suspensions of ME1207 were prepared (one using the crude powder, the other using granules) in 0.5% carboxymethylcellulose. Each suspension was administered orally (20 mg/kg) by gavage tube to female beagle dogs, that were 3-4 weeks of age. Blood samples were drawn at 0.5, 1, 2, 4, 6, 8, and 24 hours after dosing, and assayed for drug concentration.

The following pharmacokinetic parameters were obtained:

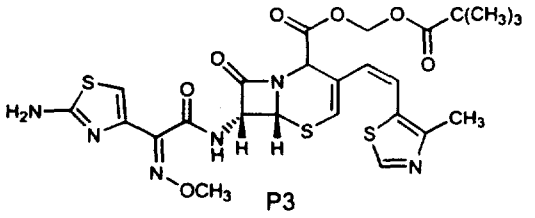
	crude powder	granule suspension
Cmax (mcg/ml):	2.56	2.91
Tmax (hours):	2	2
AUC (mcg x hrs/ml):	14.0	17.8
Vd (L/kg):	3.9	3.1
Half-life (hours):	1.90	2.06

In one-month rat and dog studies, the plasma drug levels were quite variable, and the blood levels in dogs were much lower than those in rats at comparable doses. In the one-month rat toxicokinetic study, ME1207 was administered orally by gavage to Sprague-Dawley rats (35/sex/group) at dose levels of either 0, 125, 250, or 500 mg/kg/day. In the one-month dog toxicokinetic study, ME1207 was administered orally by capsule to beagle dogs (3/sex/group) at dose levels of either 0, 63, 125, or 250 mg/kg/day for one month. The following toxicokinetic values were reported:

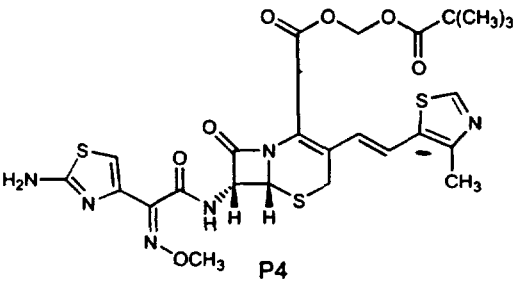
Dose (mg/kg)	Gender	Rat			Dog		
		t_{max} (h)	C_{max} (µg/mL)	AUC_{24} (µg·h/mL)	t_{max} (h)	C_{max} (µg/mL)	AUC_{24} (µg·h/mL)
63	Male	-	-	-	2.3-3.0	2.0-4.7	6.9-12
	Female	-	-	-	1.3-2.0	0.5-2.1	1.3-5.9
125	Male	1	28-45	115-150	1.3-3.3	1.9-5.5	5.5-21
	Female	1-2	22-44	48-104	2.0-3.0	5.8-9.6	14-30
250	Male	1-2	36-55	133-224	2.7-4.0	4.0-7.8	22-34
	Female	1-2	29-44	132-143	1.7-4.0	6.2-8.2	9.9-39
500	Male	2	45-58	224-384	-	-	-
	Female	1-2	39-46	163-224	-	-	-

Metabolism

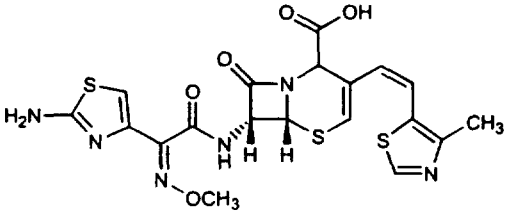
Cefditoren is not metabolized extensively. In a study in bile duct-cannulated rats, 96% of an intravenous dose was recovered unchanged in the bile and urine. Four minor metabolites, designated as P3, P4, P7, and P8, have been identified, and have the following structures:



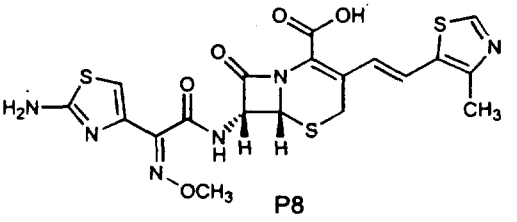
P3



P4

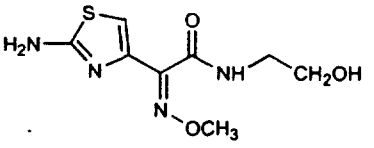


P7

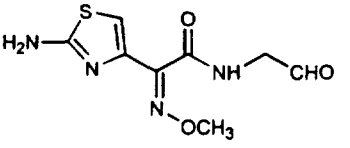


P8

Cleavage of the beta-lactam ring, results in the formation of metabolites M-OH and M-CHO, with the hydroxy metabolite being the major metabolite.



M-OH



M-CHO

Metabolites P3 and P4 were detected in feces from rats and dogs; metabolites P7, P8, and M-OH were detected in rat, dog, and human feces.

Hydrolysis of the pivoxil ester moiety resulted in the formation of pivalic (trimethylacetic) acid and formaldehyde. The pivalic acid is conjugated with either carnitine or glucuronic acid, and excreted mainly in the urine. Formaldehyde is metabolized to carbon dioxide.

Cefditoren was not an inducer of liver drug metabolizing enzymes.

Excretion

In an experiment in male mice (4/group), the 24 hour urinary excretion averaged 31.4% after intravenous administration of ME1206, and 21.6% after oral administration of ME1207. Both doses were 20mg/kg.

In rats, dogs, and humans, the majority of a radioactive dose was excreted in the feces, with smaller amounts excreted in the urine, as shown in the following table: .

	Cumulative Percent of Total Radioactive Dose								
	Rat (20 mg/kg)			Dog (20 mg/kg)			Human (400 mg)		
Time (h)	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total[a]
4	5.5	-	5.5	2.2	-	2.2	0.6	-	0.6
8	7.0	-	7.0	2.8	-	2.8	1.3	-	5.7
12	7.5	0	7.5	3.1	46.5	49.7	2.7	-	7.1
24	9.5	55.7	65.2	3.7	91.6	95.3	3.2	0	7.6
48	11.5	80.4	91.9	4.2	92.8	97.1	3.9	43.9	52.1
72	11.8	84.1	96.0	4.4	93.6	98.0	4.3	64.4	73.1
96	11.9	84.5	96.3	4.4	93.6	98.0	4.5	86.0	94.8
120	11.9	84.5	96.3	4.4	93.6	98.0	4.5	87.1	95.9

[a]Total recovery values have been corrected to account for the portion of the radioactive dose (17.4%) recovered in the vomit from one subject at approximately 8 hours after dosing.

Accumulation, Binding

The potential for accumulation was investigated in male rats. ME1207, in a dose of 20 mg/kg, was administered orally to groups of rats, for either 1, 7, or 14 days. Plasma drug levels and urinary excretion were measured. Plasma drug levels did not increase over time, indicating that the drug does not accumulate. Urinary excretion also did not increase over time.

The following values were reported for serum protein binding rates in an *in vitro* ultrafiltration method:

Mouse	89.6%
Rat	97.0%
Rabbit	99.8%
Dog	65.2%
Monkey	84.5%
Human	91.5%

TOXICOLOGY

All of the toxicology studies were conducted according to GLPs (with the exception of some minor preliminary studies). Unless specified otherwise, all rats used in the preclinical studies were of the Sprague-Dawley strain; dogs were beagles. Because of changes in the manufacturing process, several different forms of the test substance were tested in the toxicology studies, and in addition, some of the studies were repeated.

The forms of the test substance were described as follows:
Bulk Drug Powder (the complete toxicology profile was developed with this material)
ME1207 Granules (used in tablets and suspension)
Crystalline Bulk Drug Powder
Amorphous Bulk Drug Substance
ME1207-NRS (bulk drug containing new related substances)
ME1206 (used for intravenous dosing)
In general, all forms of the test substance produced similar types of effects.

Single-dose Studies

Single-dose studies were conducted in mice (Crj:CD-1 strain), rats, and dogs using intravenous and oral routes of administration. Mice and rats also received intraperitoneal and subcutaneous injections. A mortality rate of 55% occurred when mice received an intraperitoneal injection of cefditoren pivoxil at a dose of 5000 mg/kg; however, at necropsy, insoluble particles of drug were found in the abdominal cavity of these animals. No deaths occurred in mice when the compound was administered intraperitoneally at a dose of 2000 mg/kg, intravenously at a dose of 3000 mg/kg, subcutaneously at 5000 mg/kg, or orally at 5100 mg/kg.

A similar pattern was seen in rats; 85% mortality by the intraperitoneal route, but no deaths by the other routes. There were no deaths in dogs. The results of the acute studies are shown in the three following tables.

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Animal	Route	Treatment/Dose	Clinical Signs	Necropsy	Mortality	Minimum

Species		(No. of Animals per grp. M/F)		Findings	(dead/treated) per group	Lethal Dose (mg/kg)
Mouse	IP	2000 and 5000 mg/kg (10/10)	↓ Activity, respiration rate & body weight; crawling	Residual compound, Liver hypertrophy	At 5000: M: 5/10 F: 6/10 At 2000: None	>2000 mg/kg < 5000 mg/kg
Mouse	SC	2000 and 5000 mg/kg (10/10)	None	None	Both Doses: M: 0/10 F:0/10	>5000 mg/kg
Mouse	IV	3000 mg/kg (10/10)	↓ Activity and respiration; creeping, stretching, piloerection; yellowish white turbid urine	None	Male: 0/10 Female: 0/10	>3000 mg/kg
Mouse	Oral	5100 mg/kg (10/10)	None	None	Male: 0/10 Female: 0/10	>5100 mg/kg

Animal Species	Route	Treatment/ Dose (Number of animals/grp M/F)	Clinical Signs	Necropsy Findings	Mortality (dead/treated)	Minimum Lethal Dose (mg/kg)
Rat	IP	2000 and 5000 mg/kg (10/10)	↓ Activity, ↓ in body temperature and respiration rate; ↓ body weights on Day 3	Residual compound in rats that died and 1 rat at 2000 mg/kg; Splenic capsule opacification; hepatic adhesions and/or hypertrophy	At 5000 mg/kg M: 8/10 F: 9/10 At 2000 mg/kg No Deaths	>2000 mg/kg < 5000 mg/kg
Rat	SC	2000 and 5000 mg/kg (10/10)	Sclerosis or induration at injection sites	2000 mg/kg: 1/2 of rats had residual compound at injection sites 5000 mg/kg: all rats had residual compound at the injection sites	Male: 0/10 Female: 0/10 (in both groups)	>5000 mg/kg
Rat	IV	3000 mg/kg (10/10)	Decreased activity and respiration rate; abnormal gait, creeping, stretching; yellowish white turbid urine, hematuria	None	Male: 0/10 Female: 0/10	>3000 mg/kg
Rat	Oral	5100 mg/kg (10/10)	None	None	Male: 0/10 Female: 0/10	>5100 mg/kg

Animal Species	Route	Treatment/ Dose	Clinical Signs	Necropsy Findings	Mortality (dead/treated)	Minimum Lethal Dose (mg/kg)

		(No. of Animals/grp, M/F)				
Beagle Dog	IV	500 mg/kg (2/0)	None	None	Male: 0/2	>2000 mg/kg
		1000 mg/kg (2/0)	Lip licking; emesis.	None	Male: 0/2	
		2000 mg/kg (2/0)	Lip licking, emesis, white urinary sediment, ↑ prothrombin times, ↓ APTT, RBCs, hematocrit and hemoglobin values	None	Male :0/2	
Beagle Dog	Oral	500 mg/kg (4/4)	Feces contained compound on Day 2 at 500, 1000 and 2000 mg/kg; feces	None	Male: 0/4 Female: 0/4 (for each grp)	>2000 mg/kg
		1000 mg/kg (4/4)	contained compound on Day 3 at 1000 and 2000 mg/kg; water intake and	None		
		2000 mg/kg (4/4)	urine volume ↓ in all animals; slight ↑ in urinary electrolytes	None		

Acute Oral Toxicity Studies in Juvenile Rats

Four acute studies in juvenile rats were conducted, using different vehicles and forms of the test substance. ME1207 was suspended in sterile water, and administered by gavage to two groups of three-day-old Sprague-Dawley rats (5/sex/group) in a single dose of either 1000 or 2000 mg/kg. The animals were observed for two weeks, and then necropsied. This study did not include an untreated control group.

Decreased reflexes to external stimulation (external stimuli not described) were observed in 3/5 males, and 4/5 females that had received 2000 mg/kg. The decreased reflexes lasted for two hours after dosing, and then disappeared. No effects were seen in the low-dose group. There were no deaths, or any other signs of toxicity in this study.

A suspension of ME1207 powder in 0.1% carboxymethylcellulose was administered orally by gavage tube to juvenile Sprague-Dawley rats (6/sex/group) in a single dose of either 0 (control) or 5000 mg/kg. One group of rats was three days old, and another group was 21 days old. The animals were observed for 14 days after dosing.

There were no deaths or signs of toxicity in the study.

A suspension of ME1207 granules was prepared in sterile water, and administered orally by gavage tube to three-day-old Sprague-Dawley rats (5/sex/group) in a single dose of either 1000 or 2000 mg/kg. The animals were observed for 14 days after dosing.
Decreased reflexes were seen in all treated pups, for about two hours after dosing. No deaths occurred in the low-dose group, but there were two deaths (one male, one female) in the 2000 mg/kg group (20% mortality).

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