Urinalysis, Day 86: Urinary volume for male monkeys at 10 mg/kg/day was decreased to 51.7% of the control (114.0 mL). Urinary chloride levels for male monkey at 10 mg/kg/day were decreased to 36.5% of the control (52 mM). Excreted sodium and chloride for male monkeys at 10 mg/kg/day were decreased to 50.1 and 26.2% of control values (6720 and 6814 μmoles), respectively. Excreted potassium for male monkeys at 0.4, 2, and 10 mg/kg/day were decreased to 83.5, 78.6, and 68.9% of the control (5294 μmoles), respectively. Excreted sodium for female treatment groups were decreased to 58.3-76.6% of the control (7305 μmoles). Excreted potassium for female treatment groups were decreased to 49.9 to 79.6% of the control (4299 μmoles). Excreted chloride for female treatment groups were decreased to 64.9-87.1% of the control (5330 μmoles).

6. **Physical Examinations:** Electrocardiographic and ophthalmic examinations revealed no treatment-related changes.

Electrocardiogram: T wave amplitudes for female monkeys at 10 mg/kg/day on day 95 were decreased to 60.2% of the control (0.201 mV). T wave amplitudes for male monkeys at 2 and 10 mg/kg/day on days 31 and 95 were decreased as compared to the controls; however, similar differences were observed prior to the start of treatment (day -5).

7. **Organ Weights:** Increased absolute and relative spleen weights observed with SR90107A at doses of 2 and 10 mg/kg/day appeared to be related to extramedullary hematopoiesis. Decreased absolute thymus weights observed at 10 mg/kg/day may have been related to thymic involution. Increased absolute and relative liver weights were observed principally at 10 mg/kg/day, although, there were no corresponding histopathological findings. Alterations (i.e., generally decreases) in absolute and relative weights for the testes, prostate, seminal vesicles, uterus, and ovaries were observed for SR90107A treatment groups; however, there were no dose response relationships and changes were erratic.

Spleen: Absolute spleen weights for male monkeys at 0.4, 2, and 10 mg/kg/day were increased to 143.3, 128.6, and 144.3% of the control (6.75 g), respectively. Absolute spleen weights for female monkeys at 2 and 10 mg/kg/day were increased to 137.7 and 130% of the control (5.76 g), respectively. Relative spleen weights for male monkeys at 0.4, 2, and 10 mg/kg/day were increased to 113.6, 118, and 128.4% of the control (17.434 g/kg), respectively. Relative spleen weights for female monkeys at 0.4, 2, and 10 mg/kg/day were increased to 110.3, 135.4, and 146.8% of the control (1.870 g/kg), respectively.

Liver: Absolute liver weights for male and female monkeys at 10 mg/kg/day were increased to 109.8 and 108.5% of control values (85.24 and 72.22 g), respectively. Relative liver weights for male monkeys at 0.4, 2, and 10 mg/kg/day were increased to 113.6, 118, and 128.4% of the control (17.434 g/kg), respectively. Relative liver weight for female monkeys at 10 mg/kg/day was increased to 122% of the control (23.524 g/kg), respectively.

Thymus: Absolute thymus weights for male and female monkeys at 10 mg/kg/day were decreased to 68.1 and 65.7% of control values (3732 and 1976 mg), respectively.

8. Gross Pathology: Gross pathological findings at injection sites were observed in all treatment groups as well as the control group and consisted of subcutaneous hematomas and slight whitish induration in the subcutaneous tissues. Hematomas were also evident in the skin, subcutaneous tissue, abdominal cavity, and crural muscle. The incidences of hematomas were increased in SR90107A treatment groups. The spleen was grossly enlarged for 1 female monkey at 10 mg/kg/day. The thymus was grossly reduced in size for animals at 2 and 10 mg/kg/day. Petechiae were evident in the lungs for 1 female monkey at 10 mg/kg/day.

Gross pathological findings for monkeys that received SR90107A by the intravenous route at doses of 0, 0.4, 2, and 10 mg/kg/day for up to 3 months.

Organ/Tissue	0 mg/kg/day		0.4 mg/kg/day		2 mg/kg/day		10 mg/kg/day	
	Male	Female	Male	Female	Male	Female	Male	Female

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Injection Sites								
1. Right forelimb vein								
-SC hematoma	0	0	0	0	0	1	0	2
2. Left forelimb vein								
-SC hematoma	0	0	0	0	0	0	0	2
-slight whitish induration in the SC tissue	0	0	0	0	0	0	0	1
3. Right hindlimb vein								
-SC hematoma	2	3	0	1	1	3	2	3
-slight whitish induration	4	4	3	4	2	4	4	2
4. Left hindlimb vein								
-SC hematoma	0	1	2	2	2	0	1	1
-slight whitish induration	3	4	3	4	2	4	4	4
Skin & SC Tissue								
-hematomas	0	0	0	0	0	0	2	0
Abdominal Cavity								
-reddish mass along the left ventral aspect of the vertebral column	0	0	0	0	0	0	1	0
Spleen								
-irregular edges	0	0	0	0	1	0	0	1
-slightly enlarged	0	0	0	0	0	0	0	1
Mesenteric LN								
-enlarged	0	0	0	0	0	0	2	2
-moderately dark	0	0	0	0	0	0	1	0
Liver								
-slightly enlarged	0	0	0	0	0	0	0	1
Thymus								
-reduced in size	0	0	0	0	1	0	1	1
-congestion/petechiae	0	0	0	0	0	0	1	0
Lungs								
-several superficial petechiae	0	0	0	0	0	0	0	1
Crural muscle								
-pouch beneath the left thigh containing a red magma of heterogeneous consistency	0	0	0	0	0	0	0	1

9. **Histopathology**: Lesions at injection sites (i.e., serohemorrhagic or hemorrhagic infiltration, inflammatory cell infiltration, epidermal hyperplasia) were observed in all treatment groups as well as the control group; although, incidences were increased in treatment groups. These lesions were attributed to trauma of injections. The increased incidence in treatment groups was most likely due to the pharmacological activity of SR90107A. Observed changes in the popliteal lymph nodes were most likely related to changes observed at injection sites. For the spleen, reactive extramedullary hematopoiesis was evident at SR90107A doses ≥2 mg/kg/day. For the bone marrow, increased erythropoiesis was observed at SR90107A doses ≥2 mg/kg/day. Hematoma formation or hemorrhage (i.e., petechiae) was evident in several organs or tissues, principally at 2 and 10 mg/kg/day. For the mesenteric lymph nodes, macrophage infiltration was evident with SR90107A at 10 mg/kg/day.

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Histopathological findings for monkeys that received SR90107A by the intravenous route at doses of 0, 0.4, 2, and 10 mg/kg/day for up to 3 months.

Organ/Tissue	0 mg/kg/day		0.4 mg/kg/day		2 mg/kg/day		10 mg/kg/day	
	Male	Female	Male	Female	Male	Female	Male	Female

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ON ORIGINAL

Spleen								
-extramedullary erythropoiesis	0	0	0	0	0	1	3	2
Femoral bone marrow								
-increased erythropoiesis	0	0	0	0	1	1	3	4
Injection Sites								
1. Right forelimb vein								
-number examined	0	0	0	1	1	1	1	4
-hemorrhagic infiltration (hypoderm./perivasc.) slight to marked	0	0	0	0	0	1	1	1
-inflammatory cell infiltration, (hypoderm./ perivasc.) acute-subacute, fibrous	0	0	0	0	0	1	1	1
2. Left forelimb vein								
-number examined	0	1	0	0	1	0	1	4
-hemorrhagic infiltration								
hypoderm./perivasc.	0	0	0	0	1	0	0	2
dermal	0	0	0	0	0	0	0	1
-inflammatory cell infiltration								
hypodermic	0	0	0	0	0	0	1	1
dermal	0	0	0	0	0	0	0	1
3. Right hindlimb vein								
-hemorrhagic infiltration (hypoderm./perivasc.)	4	2	1	3	4	2	2	2
hematoma	0	0	0	1	0	1	0	1
dermal	0	0	1	0	0	0	0	0
-inflammatory cell infiltration								
vascular	0	2	1	0	0	0	1	0
hypoderm./perivasc.								
acute, slight	0	0	0	0	1	1	1	0
subacute/fibrous	4	4	4	4	3	4	4	3
dermal								
acute	1	0	0	0	0	2	2	0
fibrous	2	2	1	3	1	3	2	2
-epidermal hyperplasia	4	2	2	4	2	4	2	2
4. Left hindlimb vein								
-hemorrhagic infiltration (hypoderm./perivasc./ dermal)	1	3	1	3	2	2	1	2
small hematoma	0	0	0	0	1	0	0	0
-inflammatory cell infiltration								
vascular	1	0	1	0	1	0	1	0
hypoderm./perivasc.								
acute	0	0	0	0	1	0	0	0
subacute/fibrous	4	4	2	4	4	4	4	4
dermal	1	3	2	2	0	2	0	2
-epidermal hyperplasia	2	3	2	4	1	3	0	2
Popliteal LN								
-macrophages,	2	0	1	0	2	3	3	1

erythrophage, and/or sideropage infiltration (uni- or bilateral)								
Skin & SC Tissues -hematomas	0	0	0	0	1	0	2	0
Abdominal cavity -hematoma	0	0	0	0	0	0	1	0
Crural muscle -large hematoma	0	0	0	0	0	0	1	0
Hematomas -left armpit	0	0	0	0	1	0	0	0
-right armpit and abdominal hematoma	0	0	0	0	0	0	1	0
-neck hematoma	0	0	0	0	0	0	1	0
Lungs -intra-alveolar hemorrhage	0	0	0	0	0	1	1	0
Aorta -moderate perivascular hemorrhagic infiltration	0	0	0	0	0	0	1	0
Mesenteric LN -macrophage infiltration	0	0	0	0	1	0	2	2
Thymus -chronic involution	0	0	0	0	1	0	0	1
Kidneys -focal glomerular macrophage infiltration or sclerosis	0	0	0	0	1	0	1	0
-few foci of mineralization in the papilla	1	0	0	1	1	0	3	0

10. *Plasma Drug Levels*: *Plasma anti-Factor Xa activity was used as an index of* plasma drug levels. At 1 hr after dosing on days 32 or 94, plasma anti-Factor Xa activity increased with elevating dose; although, increases were generally less than proportional to dose level. Low levels of residual plasma anti-Factor Xa activity were observed 24 hr after dosing in the 2 and 10 mg/kg/day groups. Plasma anti-Factor Xa activity was not related to gender.

Plasma Anti-Factor Xa activity (IU/mL) on days 32 and 94 in monkeys that received SR 90107A by the intravenous route at doses of 0, 0.4, 2, or 10 mg/kg/day.

Dose mg/kg/day	Day 32				Day 94			
	Males		Females		Males		Females	
	Before dosing	1 hr after dosing	Before dosing	1 hr after dosing	Before dosing	1 hr after dosing	Before dosing	1 hr after dosing
0	0	0	0	0	0	0	0	0

0.4	0	1.73	0	1.93	0	1.83	0.02	2.41
2	0.04	4.82	0.03	5.10	0.04	5.03	0.07	5.58
10	0.09	13.0	0.03	10.88	0.28	19.13	0.04	13.00

In a three-month intravenous toxicology study, cynomolgus monkeys received SR90107A at doses of 0, 0.4, 2, and 10 mg/kg/day (doses expressed as salified form). The dose of 0.4 mg/kg/day could be considered a no effect dose. Mortality occurred for 1 male monkey in each the of the 0:4 and 2 mg/kg/day groups; however, these deaths appeared to be unrelated to treatment as no mortality occurred in the 10 mg/kg/day group. Target organs of toxicity appeared to be the spleen, bone marrow, and mesenteric lymph nodes. Primarily at the high dose of 10 mg/kg/day but also at the mid dose of 2 mg/kg/day, decreases in red blood cell counts, hemoglobin levels, and hematocrit were observed on days 30 and 92. Compensatory increases of the reticulocyte percentage were evident. For the spleen, reactive extramedullary hematopoiesis was evident at SR90107A doses ≥2 mg/kg/day. For the bone marrow, increased erythropoiesis was observed at SR90107A doses ≥2 mg/kg/day. Hematoma formation or hemorrhage (i.e., petechiae) was evident in several organs or tissues, principally at 2 and 10 mg/kg/day. Lesions at injection sites (i.e., serohemorrhagic or hemorrhagic infiltration, inflammatory cell infiltration, epidermal hyperplasia) were observed in all treatment groups as well as the control group; although, incidences were increased in treatment groups. These lesions were attributed to trauma of injections. The increased incidence in treatment groups was most likely due to the pharmacological activity of SR90107A. For the mesenteric lymph nodes, macrophage infiltration was evident with SR90107A at 10 mg/kg/day. Concomitant changes related to hemorrhage and hematoma formation for a few animals at 2 and 10 mg/kg/day included pallor of mucous membranes, hypothermia, decreased activity, and weakness or prostration.

REPRODUCTIVE TOXICOLOGY

SR90107A: Study of the Effects on Fertility and Early Embryonic Development in the Rat (Segment I Study) (Draft Report for Study No. FER0306).

Testing Laboratory: Sanofi Recherche
371 rue du Professeur Joseph Blayac
34184 Montpellier Cedex 04
France

Date Started: February 25, 1998

Date Completed: Unknown

GLP Compliance: Statements of compliance with GLP regulations and the quality assurance unit were included but signatures were missing.

Animals: Sprague Dawley rats were used in this study. At the start of treatment, animals were 10-12 weeks of age and body weight ranges were 362-429 g for male rats and 227-316 g for female rats.

Drug Batch: SR90107A, batch 97-01211.

Methods: The effect of SR90107A on mating performance and fertility was evaluated in rats. SR90107A was administered to rats by the subcutaneous route at doses of 0, 0.4, 2, and 10 mg/kg/day. Four injection sites were defined on the back of each animal, which consisted of 2 sites on either side of the mid-line extending from the scapular region to the lumbar region. Doses were identical to those used in general toxicity studies with the subcutaneous route. In a 4 week toxicity study, rats received SR90107A by the subcutaneous route at dose levels of 0, 0.4, 2, or 10 mg/kg/day (Study No. SDGRR 2998). The no effect level was 2 mg/kg/day. No treatment-related mortality occurred in any group. The stomach appeared to be the target organ of toxicity. For the 10 mg/kg/day group after the 4 week treatment period, 2 of 6 females were observed with mucosal edema in the forestomach. Effects observed with a dose of 10 mg/kg/day appeared to be reversible as changes in the stomach were not observed following a 16 day recovery period. Dosages of 0.4 to 10 mg/kg/day range from 8 to 200 times the proposed Phase III dose of 0.05 mg/kg. In the present study, there were 25 rats/sex/group. Control rats received the vehicle, 0.9% NaCl. The dose volume was 2.0 mL/kg. Male rats received SR90107A for 4 weeks prior to mating, throughout the mating period, and until the day preceding sacrifice for a total treatment time of 50-52 days. Female rats received SR90107A for 15 days prior to mating, throughout the mating period, and until day 7 of gestation. Animals were observed for mortality and clinical signs of toxicity at least twice daily. Male body weights were measured on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39, 43, 46, and 50. Male food

consumption was analyzed as average daily food consumption in 4 day time intervals from days 1 to 50. Female body weight was measured on days 1, 4, 8, 11, and 15 prior to mating and on days 0, 4, 8, and 13 of gestation. Female food consumption was analyzed as average daily food consumption in 4 day time intervals from days 1 to 15 prior to mating and days 0 to 13 of the gestation. Male and female rats were mated on a to one-to-one basis for a period not to exceed 3 weeks beginning on day 29 of treatment for male rats. F_0 male rats were sacrificed from day 51 onward. Necropsy examinations were performed on all male rats. For male rats, absolute weights were obtained for the testes, epididymides, prostate, and seminal vesicles. The left testes and epididymis were used for sperm analysis (i.e., counts and motility). F_0 females were sacrificed on day 14 ± 1 of gestation. Necropsy examinations were performed on all female rats. For pregnant female rats, the number of corpora lutea in each ovary was counted. The uterus was opened and number of live and dead fetuses, early and late resorption sites, and visible implantation sites were counted.

Results:

1. **Observed Effects:** Male and female rats that received SR90107A at 10 mg/kg/day were both observed with a 20% (5/25) incidence of minimal to marked hematomas at the injection site as compared to no findings for the control, 0.4 mg/kg/day, and 2 mg/kg/day groups.

2. **Mortality:** One female rat that received SR90107A at 10 mg/kg/day died on day 19 of treatment. From days 7 onward, the rat was observed with a minimal to moderate hematoma at the injection site in the left scapular region. From days 15 onward, the rat was observed with a distended abdomen, pale eyes, and pale mucosa. On day 19, the rat was observed with decreased activity and ruffled fur and subsequently sacrificed in a moribund condition. A necropsy examination found increased volumes for the spleen (marked), liver and iliac lymph nodes (moderate), and mesenteric lymph nodes (slight). Microscopic examination identified a lymphosarcoma, which was considered to be responsible for increased organ volumes.

3. **Body Weight and Food Consumption:** Body weight gain and food consumption for male rats that received SR90107A at 0.4, 2, or 10 mg/kg/day for 50 days were unaffected. Body weight gain and food consumption for female treatment groups were unaffected over the periods from days 1 to 15 prior to mating and days 0 to 13 of gestation.

4. **Fertility in F_0 Male Rats:** The mating and fertility indexes were unaffected for male rats that received SR90107A at 0.4, 2, or 10 mg/kg/day. Absolute weights for the testes, epididymides, prostate, seminal vesicles were unaffected by treatment with SR90107A. Sperm motility and sperm head count from the left caudal epididymis and testes were unaffected by treatment with SR90107A.

5. Fertility and Early Embryonic Development in F_0 Female Rats: The incidence of female rats with irregular cycles during the 15 day period prior to mating was increased to 16% (4/25) at a dose of 10 mg/kg/day as compared to 4% (1/25) for the control. However, an irregular estrous cycle appeared to have no effect on subsequent conception. The mating and fertility indexes were unaffected for female rats that received SR90107A at doses ≤10 mg/kg/day. Numbers of corpora lutea/dam, implantations/dam, live fetuses/dam, dead fetuses/dam, resorptions/dam, pre-implantation loss/dam, and post-implantation loss/dam were unaffected by treatment with SR90107A at doses ≤10 mg/kg/day.

Mating, Fertility, and Litter Parameters for female rats that received SR90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, and 10 mg/kg/day.

Dose	0 mg/kg/day	0.4 mg/kg/day	2 mg/kg/day	10 mg/kg/day
# Female rats	25	25	25	24[A]
Mating Index	100% (25/25)	100% (25/25)	100% (25/25)	100% (24/24)[A]
Fertility Index	96% (24/25)	96% (24/25)	92% (23/25)	87.5% (21/24%)
Corpora lutea/dam	16.4	16.7	16.3	16.4
Implantations/dam	14.1	15.2	14.0	14.9
Pre-implantation loss	2.3 (13.51%)	1.5 (8.91%)	1.8 (11.21%)	1.6 (8.78%)
Live Fetuses/dam	13.3	14.1	12.7	14.1
Dead Fetuses/dam	0	0	0	0
Resorptions/dam -early -late	 0.8 0.0	 1.1 0.0	 1.3 0.0	 0.7 0.0
Post-implantation loss	0.8 (5.18%)	1.1 (8.11%)	1.3 (10.18%)	0.7 (4.84%)

A. One female rat that received SR90107A at 10 mg/kg/day died on day 19 of treatment.

The effects of SR90107A on mating and reproductive performance were evaluated in rats. Rats received SR90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, and 10 mg/kg/day. Male rats received SR90107A for 4 weeks prior to mating, throughout the mating period, and until the day preceding sacrifice for a total treatment time of 50 days. Female rats received SR90107A for 15 days prior to mating, throughout the mating period, and until day 7 of gestation. SR90107A had no effects on fertility and mating performance at doses ≤10 mg/kg/day.

Embryo Toxicity Study by the Subcutaneous Route in the Rat (Segment II Study) (Report No. 693.3.041).

Testing Laboratory: [redacted]

Date Started: November 25, 1997

Date Completed: September 21, 1998

GLP Compliance: Statements of compliance with GLP regulations and the quality assurance unit were included.

Animals: Pregnant female Sprague Dawley rats were used in this study. On day 0 of gestation, female rats were 10-12 weeks of age and had a body weight range of 199-261 grams.

Drug Batch: SR90107A, batch D007036/97-01211.

Methods: The teratogenic potential of SR90107A was assessed in pregnant female rats. Rats received SR90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, and 10 mg/kg/day from days 6 to 17 of gestation. Rats in the control group received the vehicle, 0.9% sterile isotonic saline for injection. There were 25 pregnant female rats per group. The dose volume was 2.0 mL/kg. Injections were performed over six different sites on the back of each rat. Doses were identical to those used in general toxicity studies with the subcutaneous route as described earlier. In the present study, rats were observed twice daily for morbundity/mortality. Rats were observed for clinical signs of toxicity twice daily, before and after dosing. Body weights were measured on days 0, 6, 11, 15, 18, and 20 of gestation. Rats were sacrificed on day 20 of gestation and examined for macroscopic pathological changes in maternal organs. Any abnormal tissues were collected for possible histopathological analysis. The ovaries and uterus were removed and examined. The placenta was also examined. The following information was collected: pregnancy status, number of corpora lutea, number and distribution of intrauterine implantations, number of live and dead fetuses, late intrauterine deaths (resorptions), early intrauterine death (resorption sites), individual fetal weights, individual placental weights, and fetal sex. Intrauterine deaths were classified on the basis of the presence (late) or absence (early) of fetal or decidual tissue in addition to placental tissue. Each fetus was examined for external defects and then sacrificed. Approximately one-half of each litter was examined for visceral anomalies and then eviscerated. The eviscerated fetal carcasses were fixed and processed for skeletal examination. The remaining fetuses were processed for fixed visceral examination and observed using low power magnification.

Results:

1. **Observed Effects in Pregnant F_0 Female Rats**: The incidence of subcutaneous dark red area(s) at injection site(s) was increased in the 10 mg/kg/day group. The incidence of subcutaneous dark red area(s) observed at 1 of 6 injection sites was as follows: control, 1; 0.4 mg/kg/day, 0; 2 mg/kg/day, 2; and 10 mg/kg/day, 11. One female at 10 mg/kg/day had a subcutaneous dark areas at 2 of 6 injections sites. A soft and movable mass at one injection site was found for 1 female at 10 mg/kg/day.

2. **Mortality in Pregnant F_0 Female Rats**: None.

3. **Body Weight and Food Consumption in Pregnant F_0 Female Rats**: Body weight gains and food consumption were unaffected for SR90107A-treated dams.

4. **Embryo-Fetal Development in F_1 Fetuses:** SR90107A had no effects on any reproductive or litter parameters evaluated including: corpora lutea, implantation sites, total fetuses, live fetuses, dead fetuses, resorptions, pre-implantation loss, and post-implantation loss. Fetal body weights and placental weights were also unaffected. There were no treatment-related external or visceral malformations or variations. There were no treatment-related skeletal malformations. External and skeletal examination of 1 fetus from the 10 mg/kg/day group revealed gastroschisis, acaudia, and a malformed vertebral column; although, the incidence at 1 of 294 fetuses (0.3%) suggested a background event. The MARTA Historical Control Project for Sprague Dawley rats (1988-1992) listed a background incidence for gastroschisis of 0.01%; although, background incidences were not available for acaudia and a malformed vertebral column (Handbook of Developmental Toxicology, Editor: R.D. Hood, CRC Press, New York, 1997). The incidence of shortened 13th rib(s), a skeletal variation, was observed with a higher frequency at 2 and 10 mg/kg/day.

Reproductive and litter parameters for pregnant F_0 female rats that received SR90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, and 10 mg/kg/day from days 6 to 17 of gestation.

Dose, mg/kg/day	**0**	**0.4**	**2**	**10**
Number of inseminated female rabbits	25	25	25	25
Number of pregnant rabbits	24 (96%)	23 (92%)	23 (92%)	24 (96%)
Number of pregnant rats with live fetuses on day 20 of gestation	24	23	23	24
Gravid uterus weight, g (% of control)				
Corpora lutea/dam	16.6 (398/24)	15.6 (359/23)	14.4 (331/23)	15.0 (359/24)
Implantations/dam	14.1 (338/24)	14.2 (326/23)	12.5 (287/23)	13.3 (320/24)
Live fetuses/dam	12.9 (309/24)	13.2 (304/23)	11.5 (265/23)	12.3 (294/24)
Dead fetuses/dam	0	0	0	0
Pre-implantation loss, %	13.9	8.9	17.0	12.1
Resorptions/dam -Total -Early -Late	 1.2 (29/24) 1.2 0 (1/24)	 1.0 (22/23) 1.0 0	 1.0 (22/23) 1.0 0	 1.1 (26/24) 1.0 (25/24) 0.0 (1/24)
Post-implantation loss, %	9.0	7.0	7.3	8.3
Sex Ratio (M:F)	46%:54% (141/168)	48%:52% (146/158)	50%:50% (132/133)	51%:49% (149/144)
Fetal Weight, g -male -female	 4.10 3.87	 4.29 4.08	 4.18 3.97	 4.31 4.06
Placental Weight, g -male -female	 0.52 0.51	 0.53 0.52	 0.54 0.58	 0.56 0.54

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External malformations for F_1 fetuses derived from F_0 dams that received SR-90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, or 10 mg/kg/day from days 6 to 17 of gestation [Fetal Incidence (%Fetal Incidence)/Litter Incidence (%Litter Incidence)].

Dose, mg/kg/day	0	0.4	2	10
Fetuses/Litters evaluated	309/24	304/23	265/23	294/24
Vertebral column: malformed	0	0	0	1 (0.3%)/ 1 (4.2%)
Apodia	0	0	0	1 (0.3%)/ 1 (4.2%)
Gastroschisis	0	0	0	1 (0.3%)/ 1 (4.2%)
Acaudia	0	0	0	1 (0.3%)/ 1 (4.2%)

Fetal external variations for F_1 fetuses derived from F_0 dams that received SR-90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, or 10 mg/kg/day from days 6 to 17 of gestation [Fetal Incidence (%Fetal Incidence)/Litter Incidence (%Litter Incidence)].

Dose, mg/kg/day	0	0.4	2	10
Fetuses/Litters Evaluated	309/24	304/23	265/23	294/24
Placental twin	0	4 (1.3%)/ 2 (8.7%)	2 (0.8%)/ 1 (4.3%)	0
Umbilicus: Small	0	0	0	1 (0.3%)/ 1 (4.2%)

Fetal soft tissue variations for F_1 fetuses derived from F_0 dams that received SR-90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, or 10 mg/kg/day from days 6 to 17 of gestation [Fetal Incidence (%Fetal Incidence)/Litter Incidence (%Litter Incidence)].

Dose, mg/kg/day	0	0.4	2	10
Fetuses/Litters Evaluated	147/24	147/23	126/21	140/24
Kidney(s): Renal Pelvic Dilatation	3 (2.0%)/ 3 (13%)	4 (2.7%)/ 3 (13%)	3 (2.4%)/ 3 (14%)	7 (5.0%)/ 4 (17%)

Fetal skeletal malformations and variations for F_1 fetuses derived from F_0 dams that received SR-90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, or 10 mg/kg/day from days 6 to 17 of gestation [Fetal Incidence (%Fetal Incidence)/Litter Incidence (%Litter Incidence)].

Dose, mg/kg/day	0	0.4	2	10
Fetuses/Litters evaluated	162/24	157/23	139/23	154/24
Fetal Malformations				
Vertebral column: malformed	0	0	0	1 (0.6%)/ 1 (4.2%)
Limbs: malformed	0	0	0	1 (0.6%)/ 1 (4.2%)
Fetal Variations				
Frontals: Incomplete ossification	0	0	1 (0.7%)/ 1 (4.3%)	0
Hyoid: Not Ossified	3 (1.9%)/ 3 (13%)	0	2 (1.4%)/ 2 (8.7%)	4 (2.6%)/ 2 (8.3%)
Vertebra(e), Lumbar: Incomplete Ossification of Centrum	2 (1.2%)/ 2 (8.3%)	0	0	3 (1.9%) 3 (13%)

Vertebra(e), Lumbar: Number = 5	0	0	1 (0.7%)/ 1 (4.3%)	1 (0.6%)/ 1 (4.2%)
Vertebra(e), Caudal: Unossified	2 (1.2%)/ 1 (4.2%)	0	5 (3.6%)/ 1 (4.3%)	0
General: Generalized Incomplete Ossification	2 (1.2%)/ 1 (4.2%)	0	5 (3.6%)/ 1 (4.3%)	0
Limbs: Incomplete ossification of metatarsals	0	0	1 (0.7%)/ 1 (4.3%)	0
Ribs: Number of full ribs = 14/14	2 (1.2%)/ 2 (8.3%)	1 (0.6%)/ 1 (4.3%)	1 (0.7%) 1 (4.3%)	4 (2.6%)/ 3 (13%)
Ribs: Wavy	0	0	1 (0.7%)/ 1 (4.3%)	0
Ribs: 12th Eight Unossified (13th present)	0	0	1 (0.7%)/ 1 (4.3%)	0
Ribs: Bent	0	0	1 (0.7%)/ 1 (4.3%)	1 (0.6%)/ 1 (4.2%)
Ribs: 13th Shortened	0	0	2 (1.4%)/ 1 (4.3%)	6 (3.9%)/ 3 (13%)

The teratogenic potential of SR90107A was assessed in pregnant female rats. Rats received SR90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, and 10 mg/kg/day from days 6 to 17 of gestation. SR90107A at doses ≤10 mg/kg/day was not teratogenic in rats. There were no treatment-related external or visceral malformations or variations. There were no treatment-related skeletal malformations. The incidence of shortened 13th rib(s), a skeletal variation, was observed with a higher frequency at 2 and 10 mg/kg/day.

Study title: **Study of the Effects of SR90107A on Pre- and Postnatal Development (Including Maternal Function) in the Rat by Subcutaneous Injection.**
Study number: DPN0292
Site and testing facility: Sanofi Research
9 Great Valley Parkway
Malvern, PA
GLP compliance: A statement of compliance with GLP regulations was included.
QA- Reports Yes (X) No ( ):
Lot and batch numbers: Org 31540/SR90107A, Lot 97-01211 (sulfated pentasaccharide, decasodium salt, 1 mL ampules at 10 mg/mL).
Protocol reviewed by Division Yes ( ) No (X):

Methods:

- **Species/strain:** Crl:CD(SD)IGS BR female rats. Mated female rats were approximately 85 days old and had a body weight range of 224.0-316.1 g on day 0 of gestation.
- **Doses employed:** 0, 0.4, 2, and 10 mg/kg/day. Controls received the vehicle, sterile, isotonic saline (0.9% NaCl).
- **Route of Administration:** Subcutaneous
- **Study Design:** F_0 dams received SR90107A at subcutaneous doses of 0, 0.4, 2, and 10 mg/kg/day from day 7 of gestation to day 20 of lactation. Animals were observed for clinical signs of toxicity three time per day, once prior to dosing and twice after dosing. Body weights of F_0 dams were measured on days 0, 7, 9, 12, 15, 18, and 20 of gestation and on days 1, 4, 7, 14, and 21 of lactation. Food consumption for F_0 dams was measured on days 0-7, 7-15, and 15-20 of gestation and days 1-7, 7-14, and 14-21 of lactation. F_0 dams were observed at least three times per day from day 20 of gestation for the onset, progress, and completion of parturition. The following litter observations were determined on day 1 of lactation: litter size, number of stillborn and dead pups, number of live pups, gross abnormalities of pups, live pup sex, and individual live pup weights. Litters were monitored daily for clinical signs of toxicity and mortality.

On day 21 of lactation, surviving F_0 dams were sacrificed and submitted to necropsy examination. Uteri were examined for number of implantation sites. Tissues collected for histopathological examination were preserved, processed, sectioned, and stained with hematoxylin and eosin for evaluation.

Body weights of F_1 pups were measured on days 1, 4 (pre-culling), 7, 14, and 21 postpartum, and weekly thereafter. Food consumption for F_1 rats was measured for days 22-43 postpartum and weekly thereafter until the start of cohabitation. Development was monitored in all F_1 male and female pups as follows: static righting reflex beginning on day 2 postpartum, pinna detachment beginning on day 2 postpartum, eye opening beginning on day 12 postpartum, vaginal opening beginning on day 28 postpartum (females), and balanopreputial separation beginning on day 35 postpartum. On day 4 of lactation, litters were culled to approximately 5 pups/sex/litter. On day 21 of lactation, 4 F_1 pups (2 pups/sex/litter) were selected for behavioral or reproductive evaluations. Pups culled on days 4 and 21 were submitted to necropsy examination and any gross abnormalities were preserved for possible histopathological examination.

One F_1 pup/sex/litter were selected for assessment of behavioral development (auditory startle, open field assessment, and passive avoidance). Auditory startle reflex tests were conducted on days 21 and 60. Motor activity was monitored using an open field photo beam activity system on days 35 and 70. Passive avoidance was performed on days 28 and 60 and repeated on days 35 and 67. Following 72 to 85 days, F_1 rats used in behavioral development tests were sacrificed and submitted to necropsy examination. Any tissues with gross abnormalities were collected, preserved, processed, sectioned, and stained with hematoxylin and eosin for evaluation.

One F_1 pup/sex/litter were selected for assessment of reproductive capacity. At least 14 days prior to start of mating, the stage of estrus for F_1 female rats was monitored. At approximately 80 days of age, one male and one female, non-siblings, from the same treatment group were paired. The number of days until mating was calculated for all F_1 female rats. Body weights of mated F_1 female rats were measured on days 0, 6, 9, 12, 15, 18, and 20. Food consumption for mated F_1 female rats was measured on days 0-6, 6-9, 12-15, 15-18, and 18-20 of gestation. Mated F_1 female rats were sacrificed on day 20 of gestation and submitted to necropsy examination. Pregnancy status was determined and the number of live and dead fetuses, resorptions (early or late), implantation sites, and corpora lutea were determined. Uteri, placentae, and ovaries of pregnant F_1 female rats were weighed and preserved. F_2 fetuses were weighed, sexed, and examined for external abnormalities. F_1 male rats were sacrificed following laparohysterectomies of F_1 female rats and submitted to necropsy examination. Epididymides, testes, prostate, and seminal vesicles were collected, weighed, and preserved. In addition, tissues with gross abnormalities were collected for histopathological examination.

- **Number of animals/sex/dosing group:** 22 mated F_0 female rats/group
- **Parameters and endpoints evaluated:** Perinatal and postnatal development of F1 generation rats.

Results:

- **Clinical signs:** There were no treatment-related clinical signs.

- **Mortality:** There appeared to be no treatment-related mortality. One female dam (#2322) at 2 mg/kg/day was found dead on 13 of lactation. Examination of this animal found gaseous distention in the gastrointestinal tract and marked hemorrhage in the cecum.

- **Body weight:** Body weight gains of F_0 female treatment groups from days 1 to 21 of lactation were suppressed. Body weights of control F_0 dams on days 7 and 20 of gestation were 281.6 and 377.1 g, respectively. Body weight gains of F_0 dams at 0.4, 2, and 10 mg/kg/day from days 7 to 20 of gestation were 98.1, 98.1, and 100.8% of the control, respectively. Body weights of control F_0 dams on days 1 and 21 of lactation were 287.5 and 326.6 g, respectively. Body weight gains for F_0 dams at 0.4, 2, and 10 mg/kg/day from days 1 to 21 of lactation were 79.5, 65, and 79.6% of the control, respectively.

- **Food consumption:** No treatment-related effects on food consumption for F_0 female treatment groups was evident during the periods of gestation and lactation.

- **Prenatal and postnatal development, including maternal function**
  - **In-life observations:**
    - **Dams:** There were no effects on length of gestation for F_0 female treatment groups. No difficulties during parturition were observed for F_0 female treatment groups. No F_0 female dams delivered prematurely. There were no changes in litter parameters that included count and/or percent data for implantations, pups delivered, live pups, stillborn pups, dead pups, pups found dead, and post-implantation loss.

Litter data for F_0 female dams that received SR90107A at subcutaneous doses of 0, 0.4, 2, and 10 mg/kg/day from day 7 of gestation to day 20 of lactation.

Parameter	0	0.4	2	10
Number of F_0 female rats inseminated	22	22	22	22
Number that died	0	0	1	0
Number of pregnant F_0 dams	20	22	20	21
Number of F_0 dams with total litter loss	0	0	0	0
Number of implantations per F_0 dam	14.7	16.0	14.9	14.7
Number of pups delivered per F_0 dam	13.5	14.5	14.2	14.2
Number of live pups per F_0 dam (%)	13.4 (99.2%)	14.4 (99.1%)	14.1 (99.4%)	14.0 (99.0%)
Number of stillborn pups per F_0 dam (%)	0	0	0.1 (0.3%)	0
Number of dead pups per F_0 dam (%)[a]	0.1 (0.8%)	0.1 (0.9%)	0.1 (0.3%)	0.1 (1.0%)
Number of pups found dead per F_0 dam (%)[b]	0.2 (1.0%)	0	0.1 (0.3%)	0.1 (0.9%)
Post-implantation loss, %	7.6	8.7	5.4	3.3

a. Determined at time of parturition or initial litter observation.
b. Excludes pups defined in "a".

- ***Offspring:*** *There were no treatment-related external* abnormalities observed for F_1 pups at birth. There were no treatment-related clinical signs or mortality for F_1 rats during pre-weaning and post-weaning periods. There were no treatment-related effects on viability or body weight gain for F_1 pups during the

period of lactation. There were no effects on physical development of F_1 male and female pups that included surface righting, pinna detachment, eye opening, vaginal opening (females), and preputial separation (males). There were no effects on body weight gains from days 22 to 78 or food consumption from days 43 to 78 for F_1 female rats. There were no effects on body weight gains from days 22 to 120 or food consumption from days 43 to 78 for F_1 male rats.

External abnormalities for F_1 pups.

Parameter	0	0.4	2	10
Fetuses examined/litters examined	270/20	320/22	283/20	298/20
Hematoma: head/snout	0	1 (1%)	1 (1%)	0
Eye(s): right bulge missing, microphthalmia	0	0	0	1 (1%)

Behavioral development of F_1 rats was evaluated with the auditory startle response, open field motor activity, and passive avoidance response. There were no effects on auditory startle (average response and maximum input) on days 21 and 60. Open field motor activity (i.e., number of movements) on day 35 for F_1 female rats at 10 mg/kg/day was reduced to 76.4% of controls (146.1-494.8 movements), although, there is probably little or no toxicological significance associated with this slight reduction. There were no effects on open field motor activity for F_1 female rats on day 70 or for F_1 male rats on days 35 and 70. There were no effects on the passive avoidance response for F_1 rats on days 28, 35, 60, and 67.

Reproductive development was assessed in F_1 rats. Pre-mating estrus cycles (i.e., number of times in estrus and average cycle length) over a 14-day period prior to that start of mating were unaffected for F_1 female rats. Mating and fertility indexes for female F_1 rats were unaffected. The number of days until insemination was unaffected. Body weight gains and food consumption from days 0 to 20 of gestation for mated F_1 female rats were unaffected. Number of corpora lutea, implantations, live fetuses, dead fetuses, and number of resorptions for F_1 dams were unaffected. Pre-implantation loss was increased for F_1 female treatment groups to 185.4 to 285.4% of the control (4.8%), although, there was no dose-response relationship. Percent male F_2 fetuses in control and treatment groups were unaffected. Fetal body weight and placental body weight were unaffected. There were no findings in external examinations of F_2 fetuses.

Mating and Fertility Indexes for F_1 female rats.

Parameter	0	0.4	2	10
Number of F_1 female rats	19	22	19	21
Mating Index, %	89 (17/19)	100 (22/22)	89 (17/19)	95 (20/21)
Fertility Index, %	79 (15/19)	86 (19/22)	63 (12/19)	86 (18/21)
Pregnancy Index, %	88 (15/17)	86 (19/22)	71 (12/17)	90 (18/20)
F_1 dams with viable litters, %	93 (14/15)	100 (19/19)	100 (12/12)	100 (18/18)

Cesarean section data for mated F_1 female rats on day 21 of gestation.

Parameter	0	0.4	2	10
Number of pregnant F_1 dams	15	19	12	17
Number of corpora lutea per F_1 dam	16.8	18.4	18.3	18.1
Number of implantations per	15.9	15.7	16.6	15.6

F_1 dam				
Total number of fetuses per F_1 dam	14.9	15.2	15.8	15.1
Number of live fetuses per F_1 dam (%)	14.9 (88.7%)	15.2 (96.6%)	15.8 (95.4%)	15.1 (96.7%)
Number of dead fetuses per F_1 dam	0	0	0	0
Number of resorptions per F_1 dam (%)	1.1 (11.3%)	0.5 (3.4%)	0.8 (4.6%)	0.5 (3.3%)
Pre-implantation loss, %	4.8	13.0	8.9	13.7
Post-implantation loss, %	11.3	3.4	4.6	3.3
% F_2 male fetuses	48.5	54.43	51.81	52.94
F_2 Fetal body weight, g - male - female	 3.31 3.19	 3.39 3.26	 3.67 3.48	 3.39 3.20
Placental weight, g - male - female	 0.60 0.60	 0.57 0.55	 0.59 0.56	 0.60 0.56

- **Terminal and Necroscopic Evaluations:**

- **Dams:** There were findings at gross necropsy examination for two F_0 dams that appeared to be related to the exaggerated pharmacological activity of SR90107A. Focal red discoloration of the colon in 1 dam at 0.4 mg/kg/day correlated with multifocal submucosal and focal serosal hemorrhage. For 1 F_0 dam at 10 mg/kg/day, there were findings of cecal red nodules correlated with focal serosal hemorrhage and multifocal submucosal hemorrhage and the associated red mesenteric lymph nodes had erythrocytes in the subcapsular and medullary sinuses.

- **Offspring:** There were no treatment-related findings in necropsy examinations of F_1 pups culled on day 4 or 21 or F_1 rats used in behavioral assessment. For F_1 males used in reproductive assessment, there were no changes in weights of the epididymides, prostate, seminal vesicles, and testes weights. For F1 females used in reproductive assessment, there were no changes in gravid uterine or ovarian weights.

Summary and Evaluation: In a Segment III perinatal and postnatal development study, F_0 mated female rats received SR90107A at subcutaneous doses of 0, 0.4, 2, and 10 mg/kg/day from day 7 of gestation to day 20 of lactation. There were no effects on perinatal and postnatal development at SR90107A subcutaneous doses ≤10 mg/kg/day.

Rabbits

Segment II Study of Embryo/Fetal Development in Rabbits Administered SR90107A by Subcutaneous Injection (Draft Report of Study No. TER0302).

Testing Laboratory: Sanofi Research
9 Great Valley Parkway
Malvern, PA 19355

Date Started: January 17, 1998

Date Completed: Unknown

GLP Compliance: Statements of compliance with GLP regulations and the quality assurance unit were included; however, there were no signatures.

Animals: Pregnant New Zealand White female rabbits were used in this study. On day 0 of gestation, animals were approximately 22 weeks old and the body weight range was 2.9-4.1 kg.

Drug Batch: SR90107A (batch lot 97-01211).

Methods: The teratogenic potential of SR90107A was assessed in pregnant female rabbits. Rabbits received SR90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, and 10 mg/kg/day from days 6 to 18 of gestation. Rabbits in the control group received the vehicle, 0.9% sterile isotonic saline for injection. There were 20 pregnant female rabbits per group. The dose volume was 1.0 mL/kg. Injections were performed over six different sites on the back of each rabbit. Dose selection was based upon a dose range finding in pregnant female rabbits (Study No. TEP0013). Rabbits received SR90107A by the subcutaneous route at doses of 0, 0.4, 2, and 10 mg/kg/day from either days 6 to 18 (13 days) of gestation or days 6 to 28 (23 days) of gestation. There were 3 rabbits per groups. One female from the 10 mg/kg/day group died after 23 days of treatment. Histopathological findings included a large subcutaneous hematoma at the injection site, marked discoloration of the liver, and non-collapsed and purplish lungs with foam in the bronchial tubes. Hematoma formation may be related to the pharmacological activity of SR90107A. For pregnant rabbits that received SR90107A for 23 days, histopathological evaluation of the injection site found large hematomas for 2 animals at 10 mg/kg/day; moderate to marked hemorrhagic infiltration at doses of 0.4, 2, and 10 mg/kg/day, and redness and edema for animals that received 10 mg/kg/day. There were no similar findings for animals that received SR90107A at 0.4, 2, and 10 mg/kg/day for 13 days. The sponsor combined data for rabbits of the two different periods; however, it appears that there were no treatment-related effects on any reproductive or litter parameters (i.e., corpora lutea, implantation sites, total fetuses, live fetuses, dead fetuses, resorptions, and pre- and post-implantation loss). Further, there were no treatment-related external, visceral, or skeletal malformations and variations following treatment with SR90107A at doses of 0.4, 2, or 10 mg/kg/day for 13 or 23 days. Toxicokinetic analysis revealed that SR90107A crossed the placental barrier to reach fetal tissues. The high dose of 10 mg/kg/day produces plasma SR90107A levels that are sufficient to saturate circulating antithrombin III and no further inactivation of factor Xa may be achieved with higher plasma drug levels. Subcutaneous doses of SR90107A at 0.4, 2, and 10 mg/kg/day have been used in 4 and 13 week toxicology studies with rats and primates. In the present study, rabbits were observed for clinical signs of toxicity three times per day during the dosing period, once prior to dosing and twice after dosing. Rabbits were observed once/day on days outside the treatment period. Mortality was monitored daily throughout the study. Body weights were measured on days 0, 6, 9, 12, 15, 19, 24, and 29 of gestation. Food consumption was measured daily from days 6 to 29 of gestation. On day 16 of gestation, blood for determination of plasma SR90107A concentrations was collected at 1, 2, 4, 8 and 24 hr after dosing using 4 rabbits/group/time point. Plasma SR90107A concentrations were determined by measurement of anti-Factor Xa activity. Animals were sacrificed on day 29 of gestation and subjected to gross examination of major organs and tissues. The uterine horns were opened longitudinally and the products of conception were examined. Pregnancy status and the numbers of live and dead fetuses, resorptions (early or late), and implantation sites were determined. Uteri were examined and corpora lutea of pregnant females were counted. Gravid uteri (fetal + placental contents) were weighed. Placentas of live and dead fetuses were subjected to macroscopic examination and then individually weighed.

Fetuses were weighed and sacrificed. All fetuses were examined for external anomalies and variations. Viscera from all fetuses were examined for size, structure, and position of each organ within the thorax and abdomen, and for sex determination. All fetuses were examined for skeletal malformations and variations as well as ossification following staining with Alizarin Red S.

Results:

1. **Observed Effects in Pregnant F_0 Female Rabbits:** The incidence of loose stools in SR90107A-treated dams was increased as compared to controls. The incidence of loose stools for SR90107A-treated dams was as follows: 0 mg/kg/day, 0; 0.4 mg/kg/day, 1 animal ; 2 mg/kg/day, 1 animal; and 10 mg/kg/day, 2 animals.

2. **Mortality in Pregnant F_0 Female Rabbits:** None.

3. ***Body Weight and Food Consumption in Pregnant F_0 Female Rabbits:*** Body weight gains and food consumption were unaffected for SR90107A-treated dams.

4. **Toxicokinetics in Pregnant F_0 Female Rabbits:** On day 16 of gestation, blood for determination plasma SR90107A concentration was collected at 1, 2, 4, 8 and 24 hr after dosing using 4 rabbits/group/time point. Plasma SR90107A concentrations were determined by measurement of anti-Factor Xa activity. Plasma C_{max} and AUC values for SR90107A rose with increasing dosages; however, values were not proportional to dose. Data provided in the dose range finding study with pregnant female rabbits (Study no. [redacted]0013) demonstrated that SR90107A crossed the placental barrier to reach fetal tissues.

Plasma C_{min}, C_{max}, T_{max}, and AUC values for SR90107A (anti-Factor Xa activity) in pregnant F_0 female dams on day 16 of gestation.

Dose, mg/kg/day	C_{min}, mg/L	C_{max}, mg/L	T_{max}, hr	AUC, mg*hr/L
0.4	0	1.462	1	8.149
2	0.030	6.536	1	30.955
10	0.032	17.553	1	84.106

5. **Embryo-Fetal Development in F_1 Fetuses:** SR90107A had no effects on any reproductive or litter parameters evaluated including corpora lutea, implantation sites, total fetuses, live fetuses, dead fetuses, resorptions, pre-implantation loss, and post-implantation loss. Fetal body weights and placental weights were also unaffected. The incidence of pre-implantation losses for SR90107A treatment groups were increased as compared to the control; however, there was no dose response relationship and differences were not statistically significant. There were no treatment-related external, visceral, or skeletal malformations or variations.

Reproductive and litter parameters for pregnant F_0 female rabbits that received SR90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, and 10 mg/kg/day from days 6 to 18 of gestation.

Dose, mg/kg/day	0	0.4	2	10
Number of inseminated female rabbits	20	20	20	20
Number of pregnant rabbits	18/20 (90%)	19/20 (95%)	20/20 (100%)	20/20 (100%)
Number of pregnant rabbits with live fetuses on day 29 of gestation	18/18 (100%)	19[A]/19[A] (100%)	20/20 (100%)	20/20 (100%)
Gravid uterus weight, g (% of control)	496 (100%)	505 (101.8%)	532 (107.3%)	445 (89.7%)
Corpora lutea/dam	8.8	9.3	9.7	9.2
Implantations/dam	8.2	8.1	8.6	7.5
Live fetuses/dam	7.8 (141/18)	8.0 (144/18)	8.2 (164/20)	7.1 (143/200
Dead fetuses/dam	0	0	0	0.1
Total number of fetuses/dam	7.8	8.0	8.2	7.2
Number of resorptions	0.4	0.1	0.4	0.4
Pre-implantation loss, %	6.7	12.2	11.5	18.2
Post-implantation loss, %	5.3	1.4	4.0	7.0
Viable fetuses, %	94.7	98.6	96.0	93.0
Dead fetuses, %	0	0	0	1.8
Resorptions, %	5.3	1.4	4.0	5.2
% Males	45.27	51.97	51.51	50.80
Fetal body weight, g -female -male	 44.15 45.17	 45.43 45.87	 44.80 46.07	 44.84 46.75
Placental weight, g -female -male	 5.13 5.65	 5.13 5.50	 5.36 5.77	 5.59 6.04

A. One dam from the 0.4 mg/kg/day group spontaneously delivered on day 29. These fetuses were not included for evaluation.

Gross external examination for F_1 fetuses derived from F_0 dams that received SR-90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, or 10 mg/kg/day from days 6 to 18 of gestation [Litter Incidence (% Litter Incidence)/Fetal Incidence (%Fetal Incidence)].

Dose, mg/kg/day	0	0.4	2	10
Litters/Fetuses evaluated	18/141	18/144	20/164	20/143
Hindpaws -malrotated	0	0	1(5%)/ 1(0.5%)	0

Visceral examination for F_1 fetuses derived from F_0 dams that received SR-90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, or 10 mg/kg/day from days 6 to 18 of gestation [Litter Incidence (% Litter Incidence)/Fetal Incidence (%Fetal Incidence)].

Dose, mg/kg/day	0	0.4	2	10
Litters/Fetuses evaluated	18/141	18/144	20/164	20/143
Lungs -azygous lobe (absent)	0	0	1(5%)/ 1(0.7%)	0
Eyes -circumcorneal hemorrhage	0	1(5.6%)/ 1(0.6%)	0	1(5%)/ 1(0.8%)
Kidneys -small	0	0	1(5%)/ 1(0.7%)	0
-ectopic	0	0	1(5%)/ 1(0.7%)	0
Ureters -short	0	0	1(5%)/ 1(0.7%)	0

Skeletal examination for F_1 fetuses derived from F_0 dams that received SR-90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, or 10 mg/kg/day from days 6 to 18 of gestation [Litter Incidence (% Litter Incidence)/Fetal Incidence (%Fetal Incidence)].

Dose, mg/kg/day	0	0.4	2	10
Litters/Fetuses evaluated	18/141	18/144	20/164	20/143
Incomplete Ossification				
Sternebrae -1st, bipartite	0	0	1(5%)/ 1(0.5%)	0
-5th, bipartite	0	0	0	1(5%)/ 2(1.1%)
-6th, incomplete ossification	9(50%)/ 23(17.5%)	10(55.6%)/ 20(14%)	14(70%)/ 41(26.2%)	14(70%)/ 29(21%)
-6th, unossified	0	1(5.6%)/ 1(0.6%)	3(15%)/ 5(2.5%)	3(15%)/ 5(3.2%)
-6th, bipartite	0	0	1(5%)/ 1(0.6%)	1(5%)/ 1(1%)
Hyoid Body -incomplete ossification	7(38.9%)/ 19(12.8%)	12(66.7%)/ 22(16.4%)	10(50%)/ 32(18.1%)	9(45%)/ 20(12%)
-unossified	0	0	0	1(5%)/ 1(1.7%)
Variations				
Sternebrae -3rd, fused	0	1(5.6%)/ 2(1.2%)	0	1(5%)/ 1(0.5%)
-3rd, asymmetrical	0	2(11.1%)/ 4(2.6%)	3(15%)/ 4(2.3%)	2(10%)/ 2(1%)
-4th, fused	0	1(5.6%)/ 4(2.5%)	2(10%) /2(1.1%)	2(10%)/ 2(1%)
-5th, fused	0	1(5.6%)/ 4(2.5%)	2(10%) /2(1.1%)	2(10%)/ 2(1%)
Vertebrae -thoracolumbar centra, misaligned	0	1(5.6%)/ 1(0.6%)	0	0

Sutura -nasal, calcified bodies -frontal, calcified bodies -sagittal, calcified bodies	1(5.6%)/ 2(1.4%) 0 0	2(11.1%)/ 2(1.1%) 1(5.6%)/ 1(0.6%) 0	3(15%)/ 3(1.7%) 0 1(5%)/ 1(0.6%)	1(5%)/ 2(1.4%) 0 0
Hyoid -Angulated	4(22.2%)/ 6(3.7%)	5(27.8%)/ 6(4.6%)	6(30%)/ 7(4.4%)	6(30%)/ 17(9.2%)
Ribs -extra	0	1(5.6%)/ 2(1.2%)	1(5%)/ 2(1.3%)	0
Malformations				
Vertebrae -thoracolumbar arches, fused	0	1(5.6%)/ 1(0.6%)	0	0
Skull -nasal, fused	0	1(5.6%)/ 1(0.6%)	0	0
Ribs -bifurcated -fused	0 0	1(5.6%)/ 1(0.6%) 1(5.6%)/ 1(0.6%)	0 0	0 0

The teratogenic potential of SR90107A was assessed in pregnant female rabbits. Rabbits received SR90107A by the subcutaneous route of administration at doses of 0, 0.4, 2, and 10 mg/kg/day from days 6 to 18 of gestation. SR90107A at doses ≤10 mg/kg/day was not teratogenic in rabbits., There were no treatment-related external, visceral, or skeletal malformations or variations.

GENETIC TOXICOLOGY:

Ames test. Reverse mutation assay on Salmonella typhimurium (Report 693.3.007).

Testing Laboratory: Sanofi Recherche

Study Started: February 26, 1991

Study Completed: March 18, 1991

GLP Requirements: A statement of compliance with the GLP regulations and quality assurance unit was included.

Drug Batch: SR 90107A, Batch 10.

Methods: The genotoxic potential of SR 90107A was assessed by its capacity to induce a reverse gene mutation in a bacterium: Salmonella typhimurium. Two Salmonella typhimurium tester strains, TA98 and TA100, were used in this study. Strain TA100 is highly sensitive to mutagens that cause base-pair substitutions. Strain TA98 detects "frame-shift" mutations corresponding to the addition or deletion of one or more base pairs of DNA. Both strains were exposed to several concentrations of SR 90107A (10, 100, 250, 500, and 1000 µg/plate), both with and without a metabolic activation system (S-9 fraction). A set of positive controls was used to verify the reverse properties of the Salmonella typhimurium tester strains. Sodium azide (1 µg/plate) and 2-nitrofluorene (2.5 µg/plate) are direct-acting mutagens that do not require metabolic activation. 2-Aminoanthracene (1 µg/plate for TA100 and 2.5 µg/plate for TA98) requires metabolic activation before interacting with DNA. Bacterial toxicity (reduced numbers of revertant colonies/plate and sparsity of bacterial background lawn when compared to control plates) was assessed during the genotoxicity test. A compound is considered genotoxic if, at concentrations tested, the number of revertant colonies is at least twice that of spontaneous revertants, in a dose-related pattern, or if the number of revertants/nanomole is higher than 0.01, and if the positive response is reproducible.

Results: No toxic effect was observed whatever the concentration of SR 90107A tested with or without metabolic activation on either strain. SR-90107 was found to be negative in the Ames test suggesting this compound does not possess in vitro genotoxic potential.

Table 24. Ames Test without metabolic activation (without S-9 mix) (Adapted from sponsor's table in Report 693.3.007).

	TA98	TA100
Water	34.3 ± 02.67	138.3 ± 10.2
Positive Control	508.5 ± 60.5	606.5 ± 52.5
SR 90107A, 10 µg/ml	37.0 ± 2.52	118 ± 8.74
SR 90107A, 100 µg/ml	46.0 ± 1.53	122.7 ± 11.32
SR 90107A, 250 µg/ml	39.7 ± 1.76	130.0 ± 16.09
SR 90107A, 500 µg/ml	43.0 ± 2.65	119.7 ± 12.02
SR 90107A, 1000 µg/ml	37.7 ± 6.89	118.3 ± 10.17

Table 25. Ames Test with metabolic activation (with S-9 Mix) (Adapted from sponsor's table in Report 693.3.007).

	TA98	TA100
Water	45.0 ± 3.06	142.3 ± 12.86
Positive Control	858.5 ± 156.5	807.5 ± 71.5
SR 90107A, 10 µg/ml	36.3 ± 4.1	148.3 ± 8.74
SR 90107A, 100 µg/ml	37.0 ± 3.61	143.3 ± 12.33
SR 90107A, 250 µg/ml	36.7 ± 4.67	152.0 ± 8.0
SR 90107A, 500 µg/ml	39.3 ± 5.46	153.3 ± 9.24
SR 90107A, 1000 µg/ml	42.3 ± 8.84	145/3 ± 9.49

SR-90107 was found to be negative in the Ames test suggesting this compound does not possess in vitro genotoxic potential.

A bacterial microsome mutagenicity test (Ames Test) in Salmonella Typhimurium and Escherichia Coli with Org 31540 (= SR90107A) (SDGRR 4346).

Testing Laboratory: Organon

Study Started: October 4, 1995

Study Completed: April 3, 1996

GLP Requirements: A statement of compliance with the GLP regulations and quality assurance unit was included.

Drug Batch: Org 31540/SR 90107A, —— No. 395/0038, Batch No. RM1 18.

Methods: A bacterial microsome mutagenicity test (Ames Test) in Salmonella typhimurium and Escherichia coli was performed to assess the possible mutagenic potential of Org 31540. Org 31540 was tested at concentrations of 40, 200, 1000, 2500, and 5000 µg/plate in presence and absence of a metabolic activation system (± S-9 activation mix) with Salmonella typhimurium strains (TA98, TA100, TA1535, TA1537) and in an Escherichia coli strain (WP2 uvrA pKM101. The Salmonella typhimurium strains used possess different kinds of mutations at the histidine locus: strains TA100 and TA1535 have a base-pair substitution and strains TA98 and TA1537 have a frame shift mutation. The Escherichia coli strain used, strain WP2 uvrA pKM101, possess a mutation at the

tryptophan locus: a base-pair substitution. Positive controls were 2-acetylaminofluorene (25 μg/plate) for strain TA98 and TA100, 2-aminoanthracene (2 μg/plate) for strain TA1535 and WP2 uvrA pKM101 and benzo(a)pyrene (5 μg/plate) for strain TA1537. The data were evaluated only if: the number of bacteria plated was > 5 x 10^7/plate; the number of spontaneous revertants was within the normal control range in the absence of S-9 mix; and the tester stains, exposed to the positive control in the presence of S-9 mix, showed a more than two-fold increase in the number of revertants and exceeded the lower limit of the control values. The criteria for the assessment of the mutagenic potential were the presence of a relationship between dose and the number of revertants and the relative increase in the number of revertants (a two-fold increase was used as the standard for a positive response).

Results: Org 31540/SR-90107 was found to be negative in the Ames test suggesting this compound does not possess in vitro genotoxic potential. The sponsor did not use a positive control for tests without metabolic activation.

Table 26. Ames Test with or without metabolic activation (± S-9 Mix) (Adapted from sponsor's table in SDGRR 4346).

	TA98		TA100		TA1535		TA1537		E.coli	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Saline	22	26	145	159	10	13	15	13	123	171
Org 31540 40	23	27	140	151	12	12	15	15	141	191
Org 31540 200	21	27	136	145	7	11	15	13	123	153
Org 31540 1000	22	26	132	159	10	13	17	15	121	162
Org 31540 2500	20	32	136	143	9	8	17	12	136	136
Org 31540 5000	19	27	152	160	14	12	13	10	138	169
Posit. Cont.	16	1146	142	790	7	333	12	128	121	1152

Org 31540/SR-90107 was found to be negative in the Ames test suggesting this compound does not possess in vitro genotoxic potential. The sponsor did not use a direct-acting mutagen in tests without metabolic activation.

APPEARS THIS WAY
ON ORIGINAL

Ames Test – Reverse Mutation Assay on Salmonella Typhimurium Performed with SR90107A Batch 7037PT (Freeze-Dried Form of Batch 7R90018) and SR90107A Batch 980409CA-LYO (Freeze-Dried Form of Batch 97-01044) (Amendment #077; Reports 693.3.043 and 693.3.044).

Testing Laboratory: Sanofi Recherche
371 rue du Professeur Joseph Blayac
34184 Montpellier Cedex 04
France

Date Started: Report 693.3.043 August 5, 1997
Report 693.3.044 May 26, 1998

Date Completed: Report 693.3.043 December 21, 1998
Report 693.3.044 December 22, 1998

GLP Compliance: Statements of compliance with GLP Regulations and the Quality Assurance Unit were included in both reports.

Drug Batch: These studies were performed with the following:

1. SR90107A Batch numbers 7037PT (freeze-dried form of batch 7R90018). SR90107A Batch number 7037PT is the freeze-dried form obtained following ——— of the drug substance batch 7R90018. SR90107A Batch number 7R90018 contained an excessive percentage of the impurity at 1.32 relative retention time (RRT) —, whereas the maximum percentage specified was —. This impurity appears in the corresponding drug product prefilled syringes batch number D006912/ 97-01044 at RRT 1.31 around —— Based upon results of this assay, the specification of this impurity was revised from ———

2. SR90107A Batch number 980409CA-LYO (Freeze-dried form of Batch number 980410CA-AUT, obtained after ——— Batch number 97-01044). SR90107A Batch number 97-01044 contained a new impurity at 0.78-0.79 RRT. This impurity was generated from Batch number 97-01044 after ——— (Batch number 980410CA-AUT) and freeze-drying (Batch number 980409CA-LYO).

Methods: The genotoxic potentials of SR90107A Batch number 7037PT freeze-dried form and SR90107A Batch number 980409CA-LYO were assessed in bacterial reverse mutation assays using Salmonella typhimurium tester strains, TA98, TA100, TA102, TA1535, and TA1537, in the presence and absence of metabolic activation. The plate incorporation-technique was used to assess the mutagenicity of SR90107A Batch

In Vitro Gene Mutation Assay at the Locus TK+/- in Mouse Lymphoma L5178Y Cells (Amendment #034; Amendment 693.3.036).

Testing Laboratory: Department of Toxicology
Sanofi Recherche
371 rue du Professeur Blayac
34184 Montpellier Cedex 04
France

Study Started: March 5, 1996

Study Completed: March 5, 1997

GLP Requirements: Statements of compliance with GLP regulations and the Quality Assurance Unit were included.

Drug Batch: SR90107A (sodium salt), Batch numbers 5ARP007, 5ARP008, and 5ARP009.

Methods: The genotoxic potential of SR90107A was assessed by evaluating its capacity to induce a forward gene mutation at the thymidine kinase (TK) locus of mouse lymphoma L5178Y cells in the presence or absence of metabolic activation. The S-9 metabolic activation system was prepared liver of male Sprague Dawley rats treated once by the intraperitoneal route with Aroclor 1254 or pentachlorobiphenyl at a dose of 500 mg/kg. The positive controls were methyl methane sulfonate and cyclophosphamide in the absence and presence of metabolic activation, respectively. No cytotoxicity tests were conducted given the lack of toxicity observed in the human lymphocyte chromosomal aberration assay with a SR90107A concentration of 5000 µg/mL. In the first mutagenicity test, cells were treated with SR90107A at concentrations of 50, 100, 500, 1000, 2500, and 5000 µg/mL for 4 hr in the presence or absence of S-9. In a second study, cells were treated with SR90107A at concentrations of 500, 1000, 2500, and 5000 µg/mL for 20 hr in the absence of S-9. Following treatment with SR 90107A, cells were washed, and transferred to tubes for phenotypic expression of mutation over a 48-hr period. After the expression period, morphological observation of cultures allowed cytotoxic concentrations to be discarded. Survival following treatment was assessed by incubating a diluted aliquot of cells for a 13 to 14 day period. The mutation frequency was evaluated at the end of the expression period by plating cells in medium containing 3 µg/mL trifluorothymidine and incubating plates for a 10 to 11 day period. After appropriate incubation periods, cell survival following SR90107A treatment,

viability after mutation phenotypic expression, and the mutation frequency were determined. The compound was considered genotoxic if following criteria were met: the mutation frequency of treated cultures was significantly higher than that of negative controls, a clear dose-related effect was observed, and the response was reproducible except for a clearly positive effect. An increase in the mutation frequency of small colonies (ratio of small colonies to large colonies) provides an indication as to whether or not the compound is clastogenic.

Results: No cytotoxicity was observed with SR90107A concentrations ≤5000 μg/mL in the presence or absence of S-9. Mutation frequencies for cells treated with SR90107A at concentration ≤5000 μg/mL in the presence or absence of S-9 metabolic activation were not significantly different from the solvent control. Positive controls produced characteristic responses. There was no change in the mutation frequencies of large and small colonies in the presence or absence of S-9 metabolic activation.

SR90107A was negative in the forward gene mutation assay at the thymidine kinase ($TK^{+/-}$) locus of mouse lymphoma L5178Y cells in the presence or absence of metabolic activation.

In vitro DNA repair assay on rat hepatocytes in primary culture (Report 693.3.004).

Testing Laboratory: Sanofi Recherche

Study Started: October 1, 1990

Study Completed: January 22, 1991

GLP Requirements: A statement of compliance with the GLP regulations and quality assurance unit was included.

Drug Batch: SR 90107A, Batch 10.

Methods: The potential genotoxicity of SR 90107A was assessed on freshly isolated non-replicating rat hepatocytes in primary culture. DNA damage was evaluated by measuring the incorporation of ^{3}H-thymidine in the nucleus. This incorporation represents the unscheduled DNA synthesis whose induction has been well correlated with DNA damage. For the rat hepatocyte primary culture (HPC)/DNA repair assay, a cellular suspension containing 550,000 freshly isolated cells per ml medium was inoculated at a volume of 1 ml/well in 6 well plates containing rounded coverslips and 2 ml medium. After 2 hr, wells were rinsed leaving only attached viable cells. Hepatocytes were exposed to SR 90107A (10, 50, 100, 250, 500, and 1000 µg/ml) or to standard controls in the presence of 2 ml WME containing 10 µCi/ml ^{3}H-thymidine. The positive control was 2-aminofluorene used at concentrations of 0.01 and 0.05 mM. The negative control, pyrene was tested at the single concentration of 0.1 mM. Each concentration of SR 90107A was tested in triplicate. After 18 to 20 hr incubation, HPC were washed and observed under a microscope to evaluate morphology, attachment, and spreading out of cells, as well as any potential cytotoxic effects. Each coverslip was washed, immersed in a 1% hypotonic sodium citrate solution to induce swelling of nuclei to allow for better quantitation of nuclear grains, and then fixed. Autoradiographs were prepared and then stored at 4°C for 7 days. Autoradiographs were developed and stained. Cytotoxicity of a compound was expressed by the morphological observation of cells (i.e., a reduced number of cells, cell attachment, spreading of cells) and the observation of autoradiographies (the absence of S phase cells, the absence of nuclear grains in remaining hepatocytes, hepatocytes with unswollen and deformed nuclei). A compound is considered as positive when the mean number of nuclear grains is greater in treated cultures than in controls, when the mean number of "net" nuclear grains (number of grains in the nucleus

minus number of grains in the cytoplasm) is above 3 and when the percentage of cells in repair is above 20%. If a compound is negative at the highest non toxic dose, reading is performed only for this dose and the two doses just below.

Results: Org 31540/SR 90107A (10 to 1000 µg/ml) was found to be negative in the in vitro DNA repair assay. At 1000 µg/ml, 13.3% of hepatocytes were found to be in repair, which was significantly higher than the negative control; however, the net grain count was minus 1. A positive response required a net grain count ≥ 3.

Table 23. Results of DNA Repair Assay (Adapted from sponsor's table in Report 693.3.004).

Agent	NGC	CGC	NG	%IR
Control	17.8 ± 0.5	20.8 ± 0.4	-3.0 ± 0.4	3.3
DMSO	18.1 ± 0.5	20.9 ± 0.6	-2.8 ± 0.5	5
Pyrene, 1 µM	15.6 ± 0.5	19.9 ± 0.7	-4.3 ± 0.6	3.3
2-AF, 0.5 µM	49.9 ± 1.5	17.8 ± 0.4	32.1 ± 1.3	100
2-AF, 1 µM	35.3 ± 1.4	15.9 ± 0.5	19.4 ± 1.2	100
SR-90107A 1000 µg/ml	15.1 ± 0.4	16.4 ± 0.3	-1.3 ± 0.6	13.3
SR 90107A 500 µg/ml	15.2 ± 0.4	16.8 ± 0.3	-1.6 ± 0.3	3.3
SR 90107A 250 µg/ml	16.5 ± 0.4	19.2 ± 0.4	-2.7 ± 0.5	3.3

NGC = Nuclear grain count, CGC = cytoplasm grain count, NG = nuclear grain count-cytoplasm grain count, and %IR = percentage in repair.

Org 31540/SR 90107A was found to be negative in the in vitro DNA repair assay.

An In Vitro Test for Induction of Chromosome Damage: Cytogenetic Study in Cultured Human Peripheral Lymphocytes (Amendment #034; Report 693.3.038).

Testing Laboratory: [redacted]

Study Started: February 5, 1996

Study Completed: August 8, 1997

GLP Requirements: Statements of compliance with GLP regulations and the Quality Assurance Unit were included.

Drug Batch: SR 90107A, Batch No. RMD 18

Methods: The genotoxic potential of SR90107A was assessed in the human lymphocyte chromosomal aberration assay in the presence and absence of metabolic activation. Human peripheral blood lymphocytes were incubated with phytohemagglutinin for 48 hr to stimulate cell division. The S-9 microsomal activation mix was prepared from livers of rats treated with Aroclor 1254. The positive controls were chlorambucil and cyclophosphamide in the absence and presence of metabolic activation, respectively. In preliminary toxicity tests, cells were treated with SR 90107A at concentrations ranging from 0 to 5000 μg/mL (concentrations expressed in terms of salified compound). For both the cytotoxicity and chromosomal aberrations assays, lymphocytes in the absence of S-9 were treated with SR90107A as follows: a 3 hr exposure followed by medium replacement and incubation for an additional 16 hr; a 19-hr continuous exposure, or a 43-hr continuous exposure. Lymphocytes in the presence of S-9 were treated with SR90107A as follows: a 3 hr exposure followed by medium replacement and incubation for an additional 16 or 40 hr. For assessment of cytotoxicity, at least 1000 lymphocytes per culture were examined and the mitotic index was calculated as the percentage of lymphocytes examined that were at metaphase. The chromosomal aberration assay was conducted at SR90107A concentrations of 0, 1250, 2500, and 5000 μg/mL (concentrations expressed in terms of salified compound). Three hr prior to harvesting cells, cellular division was arrested by addition of colcemid (final concentration of 0.4 μg/mL). Following harvesting, cells were fixed in methanol: glacial acetic acid (3:1) and stained with Giemsa stain. At least two slides from each culture were examined. For each slide, 100 metaphases with 46 centromeres were evaluated for the following: chromosome number, all chromosomes normal or some aberrant, specific types and numbers of aberrations, and coordinates of all metaphases with aberrant chromosomes. The test material was considered to be clastogenic under the following conditions: a statistically significant increases in the frequency of metaphases with aberrant chromosomes (excluding gap-type aberrations) at one or more concentrations, the increases exceed the historical negative control range at this laboratory, the increases are reproducible between replicate cultures and between tests, the increases are not associated with large changes in pH or osmolality of the treatment medium or extreme toxicity, and evidence of a dose-response relationship or increases at both sampling times will be considered to support the conclusion.

Results: In the preliminary cytotoxicity test, SR90107A concentrations between 8 and 5000 μg/mL did not produce significant evidence of a reduction in the mitotic index at any concentrations. In the main cytogenetic test, SR90107A in the presence or absence of metabolic activation did not produce evidence of an increase in the frequency of metaphases with aberrant chromosomes at any concentration tested (1250, 2500, or 5000 μg/mL) as compared to the solvent control at any sampling time. There was no evidence of polyploidy or endoreduplication in SR90107A- or solvent control-treated

cells. Concentrations of SR90107A at 1250, 2500, or 5000 µg/mL produced no evidence of cytotoxicity. Positive controls produced characteristic responses.

SR90107A displayed no evidence of clastogenic activity in the human lymphocyte chromosomal aberration assay in the presence or absence of metabolic activation.

Micronucleus test - In vivo genotoxicity study by the intravenous route in the rat (Report 693.3.032).

Testing Laboratory: Sanofi Recherche

Study Started: October 17, 1995

Study completed: December 1, 1995

GLP Requirements: A statement of compliance with the GLP regulations and quality assurance unit was included.

Animals: Rats, OFA-SD [redacted] Rats were approximately 6 weeks old when treatment began, and the initial body weight range was 185-234 g for males and 140-181 g for females.

Drug Batch: SR 90107A, Batch 5ARP006.

Methods: The genotoxic activity of SR 90107A was assessed in rats by the micronucleus test following a single intravenous administration at 10, 20, or 40 mg/kg. There were 12 rats of each sex for the vehicle control and SR 90107A-treated groups, and 6 rats of each sex for the positive control group. SR 90107A was administered to rats intravenously. Endoxan (cyclophosphamide) was administered intraperitoneally. A single treatment was given on day 1 of the study. Animals were killed by CO_2, 24 and 48 hr after treatment for vehicle control and SR 90107A groups. Animals treated with cyclophosphamide were killed 24 hr after administration. Femurs were removed from all treated animals and bone marrow smears taken. Slides were prepared with a nucleated-cell free bone marrow suspension. For each animal, at least 2000 polychromatic erythrocytes (PCEs) were scored for micronuclei. The incidence of micronuclei in normochromatic erythrocytes (NCEs) was determined at the same time to verify the quality of the smears. The criteria for an acceptable assay were that the mean percentage of micronucleated polychromatic erythrocytes (MPCEs) in the negative control group must not exceed 5 per 1000, and the incidence of MPCEs for the positive control group is significantly higher than for the concurrent negative control group and situated with the laboratory's historical positive control data range. A decrease in the PCE:NCE percentage indicates a medullary cytotoxicity. The criterion for a positive result were a dose-related increase in the number of MPCEs or a clear increase in the number of MPCEs at a single dose and at a single sampling time. Biological relevance of results should be considered first. Statistical significance should not be the only determination of a positive response.

Results: A statistically significant increase in the ratio of polychromatic erythrocytes to normochromatic erythrocytes was found in males treated with 20 or 40 mg/kg for 24 or 48 hr; however, there was no increase in the frequency MPCEs. The micronucleus test suggest that Org 31540/SR 90107A does not possess any clastogenic potential.

Table 27. Rat Micronucleus test (Adapted from Sponsor's table in Report 693.3.032).

		PCE/NCE, %		MNCE		MPCE	
		M	F	M	F	M	F
Control	24 h	010.8	168.4	0.2	0.1	2.3	2.1
	48 h	92.9	138.5	0.2	0.3	1.8	2.0
Endoxan 35 mg/kg	24 h	93.9	82.3	0.2	0.4	22.2	16.0
SR 90107A 10 mg/kg	24 h	85.9	180.7	0.1	0.6	2.0	2.2
	48 h	85.7	144.2	0.2	0.5	1.5	2.6
SR 90107A 20 mg/kg	24 h	156.9	172.2	0.1	0.1	2.2	1.6
	48 h	124.4	128.2	0.1	0.4	2.1	2.1
SR 90107A 40 mg/kg	24 h	163.8	122.6	0.0	0.2	2.1	2.1
	48 h	128.2	172.5	0.0	0.4	1.7	2.0

Results of the rat micronucleus test suggest that Org 31540/ SR 90107A does not possess clastogenic potential.

SPECIAL TOXICOLOGY STUDIES:

An Antigenicity Study of SR90107A/Org31540 (DIV0755)

Methods: The objective of this study was to examine the antigenicity of SR90107A/Org31540 in guinea pigs, mice and rats. The guinea pigs were administered SR90107A/Org31540 subcutaneously (0.5 and 4 mg/kg) with or without Freund's complete adjuvant once weekly for 3 weeks to sensitize the animals. In case of mice, the animals were administered SR90107A/Org31540 intraperitoneally with and without 3% aluminium hydroxide gel once weekly for 3 weeks for sensitization. Rats were passively sensitized with sera from the actively SR90107A/Org31540 sensitized mice. Ovalbumin (OVA) with adjuvant and water for injection were administered SC to guinea pigs or intraperitoneally to mice once weekly for 3 weeks for sensitization as the positive and negative control, respectively.

For active systemic anaphylaxis (ASA) response, fourteen days after the sensitization, 1 ml of challenging antigen (SR90107A/Org31540) was injected into the vein of the forelegs of actively sensitized guinea pigs. The anaphylactic signs (anxiety, tremor, sneezing, scratching, piloerection, urination, defecation, dyspnea, dyskinesia, convulsion, and death) and their degree were observed 1 hour following the injection.

For 4-hour passive cutaneous anaphylaxis (PCA) response, sera was collected from the actively sensitized guinea pigs of each group 12 days after the final sensitization. Then, the diluted sera were injected intracutaneously into 6 sites (0.1 ml/site) on the shaved backs of two guinea pigs in order to produce a passive sensitization. The challenging antigen (SR90107A/Org31540 or OVA) was injected followed by 1.0% Evans Blue solution into the vein of the forelegs of each passively sensitized animal 4 hours after the passive sensitization. The animals were sacrificed 30 minutes after the challenge and the back skins were removed and the colored spots were measured. Colored spots larger than 5 mm in diameter were regarded as positive.

For mice and rats, 48-hour PCA experiment was conducted. Sera were obtained from all actively sensitized mice 7 days after the final sensitization. The diluted sera were then injected intracutaneously into 6 sites on the shaved back of two rats to produce a passive sensitization. Each challenging antigen (SR90107A/Org31540 or OVA) was injected into the tail vein of each rat followed by 1.0% Evans Blue solution. The rats were sacrificed 30 minuets after the challenge and the colored spots were measured as stated above.

Results:

1. **ASA Response with Guinea Pigs:** No abnormalities were observed in any guinea pig of the SR90107A/Org31540 or negative control groups after challenge with SR90107A/Org31540. All animals in the positive control group (sensitized by OVA) showed anaphylactic reactions immediately after challenge with OVA and died within 4 minutes after the challenge.

2. **4-Hour PCA response with Guinea Pigs:** None of the guinea pigs passively sensitized with the sera from the SR90107A/Org31540 or negative control group, showed any color spots after the challenge with SR90107A/Org31540. The positive control showed the expected response.

3. **48-Hour PCA Response with Mice and Rats:** None of the rats passively sensitized with the sera SR90107A/Org31540 or negative control groups showed any color spots after the challenge with SR90107A/Org31540. All the rats from the positive control group showed positive color spots after challenge with OVA.

SR90107A/Org31540 does not possess antigenic properties under the conditions of the experiments.

LABELING

The annotated labeling of Xantidar generally conforms to the format specified under CFR 21, subpart B, 201.50 dated April 1, 1998. However, the following changes should be incorporated.

1. **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Sponsor's Version:

[redacted]

Evaluation: The text is in accordance with 21 CFR, 201.50, Subpart B (April 1, 1998). However, the route of administration (subcutaneous) in reproductive studies in animals should be mentioned and the sentences may be rephrased as suggested below.

Proposed Version:

No long-term studies in animals have been performed to evaluate the carcinogenic potential of

was not genotoxic in the Ames test, the mouse lymphoma cell ($L5178Y/TK^{+/-}$) forward mutation test, the human lymphocyte chromosomal aberration test or the rat micronucleus test.

[

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2. **Pregnancy**

Sponsor's Version:

Pregnancy

Teratogenic Effects

Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses up to 10 mg/kg/day, , and have revealed no evidence of impaired fertility or harm to the fetus due to fondaparinux. There are however no adequate and well controlled studies of pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

[

]

Evaluation: The text is in accordance with 21 CFR, 201.50, Subpart B (April 1, 1998). However, The route of administration (subcutaneous) in animal studies should be mentioned and the section entitled is unnecessary and should be deleted.

Proposed Version:

Pregnancy

Teratogenic Effects

Pregnancy category B

Reproduction studies have been performed in pregnant rats at subcutaneous doses up to 10 mg/kg/day (about 32 times the recommended human dose based on the body surface area) and pregnant rabbits at subcutaneous doses up to 10 mg/kg/day (about 65 times the recommended human dose based on the body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to fondaparinux. There are, however, no adequate and well-controlled

studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

4. **Nursing Mothers:**

Sponsor's Version:

[ ]

Evaluation: The text did not report the findings of preclinical distribution studies in lactating rats. In lactating SD rats, the excretion of radioactivity into milk was examined after a single IV dose of 10 mg/kg of [^{35}S]-Org31540/SR90107A (SDGRR5040). At 1 h postdose, about 0.353% of the administered dose was found per gram of milk. The sponsor should incorporate this information in the text. The last sentence ——— is unnecessary and should be deleted.

Proposed Version: Fondaparinux was found to be excreted in the milk of lactating rats. However, it is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when fondaparinux is administered to a nursing woman.

5. **Overdosage:**

Sponsor's Version:

OVERDOSAGE

Symptoms/Treatment

[

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Data obtained in patients undergoing chronic intermittent hemodialysis suggest that ——— clearance can increase by 20% during hemodialysis.

There is no antidote for

[ ]

Evaluation: The text is in accordance with 21CFR, 201.50, Subpart B (April 1, 1998). However, the first paragraph should be modified as suggested below.

Proposed Version: As with any antithrombotic agent, XantidarTM doses above the recommended regimen may lead to an increased risk of bleeding.

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Data obtained in patients undergoing chronic intermittent hemodialysis suggest that ——— clearance can increase by 20% during hemodialysis.

There is no antidote for ———. Overdosage associated with bleeding complications should lead to treatment discontinuation ——— and initiation of appropriate therapy.

SUMMARY AND EVALUATION:

Org31540/SR90107A (Xantidar™) is a new chemically synthesized sulfated pentasaccharide with antithrombotic properties. Org31540/SR90107A resembles the pentasaccharide sequence in heparin responsible for binding to antithrombin III (ATIII) with the exception of the methoxy group at its non-reducing end. Xantidar may offer some advantages over the use of heparin for the prophylaxis of thrombosis. Unlike heparin (heterogeneous mixture of sulfated polysaccharide chains obtained from various tissues of animal origin), Org31540/SR90107A is a homogenous preparation obtained through total chemical synthesis. Therefore, Org31540/SR90107A may offer more predictable pharmacokinetics compared to heparin. Org31540/SR90107A appeared to be less hemorrhagic than heparin. The chance of induction of thrombocytopenia after administration of Xantidar is much less compared to heparin, which causes heparin-induced thrombocytopenia or HIT. Xantidar was a more potent (on a weight basis), selective and showed higher bioavailability (about 100%) after SC administration than heparin (absolute bioavailability 35.5 to 41.4%). The sponsor is seeking marketing approval for Org31540/SR90107A for the prevention of venous thromboembolic events in patients undergoing major orthopedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgeries.

In this NDA, the sponsor has submitted the preclinical pharmacology and toxicology studies in support of Org31540/SR90107A (Xantidar™) injections as follows: pharmacology; absorption, distribution, metabolism and excretion studies in rats, rabbits and monkeys; acute toxicity studies in mice, rats and monkeys; 2-week IV toxicity study in rat; 4-week SC toxicity study with a 16 day recovery period in rats; 13-week IV toxicity study in rats; 2-week IV toxicity study in macaques; 4-week SC toxicity study followed by a 2-week recovery period in monkeys; 3-month IV toxicity study in the macaque; study of the effects on fertility and early embryonic development in rats; embryo toxicity study by the subcutaneous route in rats; study of the effects of SR90107A on pre- and postnatal development (including maternal function) by subcutaneous injection in rats; segment II study by SC route in rabbits; Ames test; *in vitro* gene mutation assay at the locus TK+/- in mouse lymphoma L5178Y cells; *in vitro* DNA repair assay on rat hepatocytes in primary culture; chromosome aberration assay in cultured human peripheral lymphocytes; *in vivo* micronucleus test by the intravenous route in the rat and antigenicity study in guinea pigs, mice and rats.

Pharmacology studies with Org 31540/SR 90107A were conducted in various *in vitro* and *in vivo* animal models. The *in vitro* studies have demonstrated that Org 31540/SR 90107A binds to antithrombin of different species with high affinity and enhances the inactivation of factor Xa. Org 31540/SR 90107A inhibits thrombin generation in human plasma. The effects of Org 31540/SR 90107A on other coagulation factors are weak. Org 31540/SR 90107A did not potentiate ADP or collagen-induced platelet aggregation unlike heparin. The *in vivo* studies have shown that Org 31540/SR 90107A possesses antithrombotic activity in a variety of models of experimental thrombosis. Overall, Org31540/SR90107A may offer a number of advantages over the use of heparin for the prophylaxis of thrombosis. Org31540/SR90107A is a homogeneous preparation obtained through total chemical synthesis whereas heparin is a heterogeneous mixture of sulfated polysaccharide chains obtained through extraction from various tissues of animal origin. Org31540/SR90107A does not appear to have the liability to produce antibodies

unlike heparin which, causes heparin-induced thrombocytopenia or HIT. Org31540/SR90107A showed a selective mode of action and a higher bioavailability with subcutaneous administration when compared to heparin.

The pharmacokinetics of Org 31540/SR 90107A appears to be comparable across the animal species studied. Org 31540/SR 90107A was found to be completely bioavailable in rats and rabbits and in macaques at low dose. The terminal elimination half life increased across species (ranged from 1.0 to 2.0 h in rats and rabbits and about 5 to 6 h in macaques and about 15 to 20 h in humans. The Tmax values after s.c. administration were 1 to 2 h and 1.7 h in macaque and human, respectively. The distribution studies in blood indicated that Org 31540/SR 90107A is highly bound to plasma protein (92 to 93%) and were saturated above concentrations of 2 mg/ml and less than 10% was associated with RBC. Org 31540/SR 90107A was rapidly distributed in different tissues within 24 h and placental transfer was low in rats and rabbits and small amount was excreted through rat milk. There was no evidence of metabolism of Org 31540/SR 90107A in *in vitro* and *in vivo* studies and showed little potential of interaction with hepatic drug metabolizing enzymes. Org 31540/SR 90107A was excreted almost entirely through urine in rats and macaques and <10% was eliminated through feces.

Acute toxicity studies were performed in mice, rats and monkeys. For all the species administered Org31540/SR90107A by either intravenous or subcutaneous route, the maximum dose 40 mg/kg (which is about 65, 130 and 260 times the recommended human dose based on the body surface area in mouse, rat and monkey, respectively) was found to be non-lethal in all the species. It is to be mentioned here that the study TXA0444 (single-dose IV toxicity study in the mouse) was conducted with a different batch of Org31540/SR90107A (batch no. 7R90033). The maximum non-lethal dose in this study was 40 mg/kg in male and female mice.

In a 2-week IV toxicity study (TSA0957) in rats, animals were treated with Org31540/SR90107A at 0.4, 2, and 10 mg/kg/day. The no-observed-effect-level (NOEL) was identified as 2 mg/kg/day. The target organ of toxicity could not be identified because of the absence of a dose-related response and a test-article specific effect in any organ. Foci of liver necrosis were observed with an increased frequency in the 10 mg/kg/day group, however, there was no dose-response relationship for this effect. Urobilinogen levels in the urine were significantly increased in both sexes at 10 mg/kg/day indicative of hemorrhagic or hemolytic process. In addition, significant pathological lesions were observed at the site of injection, which were attributed to the trauma aggravated by the pharmacological activity of the test compound.

In a 13-week IV toxicity study in rats, animals were treated with Org31540/SR90107A at 0.4, 2 and 10 mg/kg/day. The NOEL was established as 2 mg/kg/day. The target organ of toxicity appeared to be the adrenal gland (cortical cell vacuolation in the zona fasciculata in 2 of 10 male rats at 10 mg/kg/day). This 13-week i.v. toxicity study may be used in the absence of 13-week s.c. toxicity study in rats because of the comparable pharmacokinetic parameters after a single i.v. ($AUC_{0-\alpha}$: 2.07 μg.h/ml; $T_{1/2\beta}$: 0.93 h; clearance: 146.2 ml/h/kg; volume of distribution: 178.3 ml/kg) and s.c. ($AUC_{0-\alpha}$: 2.38 μg.h/ml; $T_{1/2\beta}$: 0.95 h; clearance: 126.6 ml/h/kg; volume of distribution: 144.3 ml/kg) administration of Org31540/SR90107A in rats.

In a 4-week SC toxicity study in rats, animals were administered Org31540/SR90107A at 0.4, 2 and 10 mg/kg/day. The NOEL was established as 2 .0 mg/kg/day. The target organ of toxicity could not be identified in the absence of any significant target organ toxicity. However, 2 of 6 females showed mucosal edema in the forestomach at 10 mg/kg/day dose.

In a 2-week IV toxicity study in cynomolgus monkeys, animals were treated with Org31540/SR90107A at 0.4, 2 or 10 mg/kg/day. The NOEL was established as 2.0 mg/kg/day. Histopathological changes were observed in the kidney (chronic cortical inflammatory cell infiltration or slight focal or multifocal tubulo-interstitial nephritis in two males at each dose level with no incidence in the control group), thymus (involution in 1 control female, 2 male at low dose, 1 male and 1 female at mid-dose and 2 males and 2 females at high dose), popliteal lymph nodes (slight to moderate macrophage and erythrophage infiltration in all dose levels including control), stomach (multifocal or zonal fibrosis with atrophy at all dose levels including control), and mesenteric lymph nodes (slight macrophage or siderophage infiltration at all dose levels including control). The kidney may be considered as the target organ of toxicity.

In a 4-week SC toxicity study in cynomolgus monkeys, macaques were administered Org31540/SR90107A at 0.4, 2, and 10 mg/kg/day. The NOEL was established as 2 mg/kg/day. There was no target organ of toxicity. However, the incidence of histopathological changes in the testes, prostate and epididymis were higher in the males at 10 mg/kg. However, some of these changes were also seen in the control.

In a 3-month IV toxicity study in cynomolgus monkeys, animals received Org31540/SR90107A at 0.4, 2 and 10 mg/kg/day doses. The low dose (0.4 mg/kg/day) may be considered as NOEL. Target organ of toxicity appeared to be spleen (reactive extramedullary hematopoiesis at doses ≥ 2.0 mg/kg/day), bone marrow (increased erythropoiesis at doses ≥ 2.0 mg/kg/day) and mesenteric lymph node (macrophage infiltration in 1 male at 2 mg/kg/day and in 2 male and 2 female at 10 mg/kg/day). In addition, lesions (serohemorrhagic or hemorrhagic infiltration, inflammatory cell infiltration, epidermal hyperplasia) attributed to the trauma of injections were observed in all treatment groups including the controls. This 13-week i.v. toxicity study may be used in the absence of 13-week s.c. toxicity study in monkeys because of the comparable pharmacokinetic parameters after a single i.v. ($AUC_{0-\alpha}$: 128.77 μg.h/ml; $T_{1/2}$: 5.7 h; clearance: 0.0603 L/h/kg; volume of distribution: 0.487 L/kg) and s.c. ($AUC_{0-\alpha}$: 108.262 μg.h/ml; $T_{1/2}$: 5.7 h) administration of Org31540/SR90107A in monkeys.

In a fertility and early embryonic development study in rats (Segment I), animals were treated with Org31540/SR90107A subcutaneously at 0.4, 2 and 10 mg/kg/day. Org31540/SR90107A did not show any adverse effects on fertility and reproductive performance at any of the tested doses.

The teratogenic potential of Org31540/SR90107A was examined in pregnant female rats. The animals received Org31540/SR90107A subcutaneously at 0.4, 2, and 10 mg/kg/day from gestation day 6 to 17. No treatment-related external or visceral malformations or variations were observed. There were no treatment-related skeletal malformations. Org31540/SR90107A was not teratogenic at doses ≤ 10 mg/kg/day.

The teratogenic potential of Org31540/SR90107A was also examined in pregnant female rabbits. In this study, pregnant rabbits were administered Org31540/SR90107A at 0.4, 2, and 10 mg/kg/day subcutaneously from gestation days 6 to 18. Org31540/SR90107A did not cause any external, visceral, or skeletal malformations or variations at any of the tested doses. Org31540/SR90107A was not teratogenic in rabbits at ≤ 10 mg/kg/day.

In the Segment III perinatal and postnatal developmental study in rats, F0 mated female rats were treated subcutaneously with Org31540/SR90107A at 0.4, 2.0 and 10 mg/kg/day from gestation day 7 to day 20 of lactation. Org31540/SR90107A did not show any effect on reproductive parameters (length of gestation, number of implantations, pups delivered, live pups, post-implantation loss etc.) for F0 females. There were no treatment-related external abnormalities for F1 pups at birth. Org31540/SR90107A did not show any effect on behavioral development of F1 pups evaluated with auditory startle response, open field motor activity, and passive avoidance response. The reproductive development of F1 pups was also not affected by Org31540/SR90107A treatment. Overall, there were no effects on perinatal and postnatal development of rats after treatment with Org31540/SR90107A at subcutaneous doses ≤ 10 mg/kg/day.

In *in vitro* mutagenicity test in Ames assay, Org31540/SR90107A (batch numbers: 10, RM1 18, 7037PT, 98049CA-LYO, W) was found to be negative at 10 to 5000 µg/plate concentrations under the conditions of the assay. Org31540/SR90107A (batch numbers: 5ARP007, 5ARP008, 5ARP009 and 98-0702-CA) was negative in the forward gene mutation assay at the thymidine kinase ($TK^{\pm}$) locus of mouse lymphoma L5178Y cells in the presence or absence of metabolic activation. Org31540/SR90107A was found to be negative in the *in vitro* DNA repair assay on rat hepatocytes in primary culture at concentration range of 10 to 1000 µg/ml. Org31540/SR90107A (batch numbers: RMD 18 and W) did not show any clastogenic activity in the human lymphocyte chromosomal aberration assay in the presence or absence of metabolic activation. In the *in vivo* intravenous rat micronucleus test at 10, 20, and 40 mg/kg doses, Org31540/SR90107A was not found to be clastogenic.

The antigenicity of Org31540/SR90107A was tested using active systemic anaphylaxis (ASA) and passive cutaneous anaphylaxis (PCA) assays in guinea pigs and SD rats. Org31540/SR90107A did not induce any anaphylactic reactions in ASA test and no skin blue spots in the PCA assay. Org31540/SR90107A does not appear to possess antigenic potential.

The labeling of fondaparinux conforms to the format specified under CFR 21, Subpart B, 201.50 dated April 1, 1998. However, the suggested changes described in the text, should be incorporated.

Org31540/SR90107A has been adequately studied and well characterized pharmacologically and pharmacokinetically in different animal models. Toxicological studies have been performed in rats and monkeys up to 3 months duration, which is adequate for the marketing approval of Xantidar for the treatment duration of 7 to 11 days. There were no target organ of toxicity in rats, however, the kidney may be considered as the target organ of toxicity in monkeys. In addition, genotoxic and reproductive liability of Org31540 have also been tested in appropriate *in vitro*

and *in vivo* studies. Overall, this NDA contains adequate studies for the marketing approval of Org31540 and appears to be safe for the proposed use.

RECOMMENDATIONS:

1. From a preclinical standpoint, this NDA may be approved for the indications in which it will be used for a short period of 7 to 11 days.

2. The sponsor should be asked to change the proposed label of Xantidar™ as suggested in the text of the review.

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Tamal K. Chakraborti, Ph.D. Date
Pharmacologist, HFD-180

Comment:

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Jasti B. Choudary, B.V. Sc., Ph.D. Date
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APPEARS THIS WAY
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cc:
Original NDA
HFD-180
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HFD-180/Dr. Choudary
HFD-045/Dr. Viswanathan

R/D Init. JChoudary: 6/26/01

TC/deg: 7/2/01

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/s/

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