CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 21-492

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-492
Review number: 1
Information to sponsor: Yes ( ) No ( )
Sponsor and/or agent: Sanofi-Synthelabo Inc.
9 Great Valley Parkway
Malvern, PA 19355

Reviewer name: Wendelyn J. Schmidt, Ph.D.
Division name: Division of Oncology Drug Products
HFD #: 150
Review completion date: 5/13/02

Drug:

Trade Name: Eloxatin® for Injection (Eloxatine®, Dacplat®)

Generic Name: Oxaliplatin, Oxalatoplatin, Oxalato-platinum, DACH-oxalate

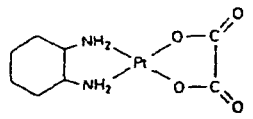
Code Name: SR96669, L-OHP, l-OHP, NSC-266046, NSC-271670, JM-83, PR 54780, 1670 RB7

Chemical Name: *cis*-[(1*R*,2*R*)-1,2-cyclohexanediamine-*N*,*N*'] [oxalato(2-)-*O*,*O*] platinum 1,2-diaminocyclohexane (DACH)

CAS Number: 61825-94-3

Molecular Formula/ Weight: $C_8H_{14}N_2O_4Pt$ / 397.3

Structure:



Oxaliplatin (l-OHP)

Related INDs/NDAs/DMFs: IND [redacted] NDA 21-063 (previously withdrawn)

Drug class: Platinum antineoplastic

Indication: Not currently available. The sponsor has not yet submitted the proposed labeling as the clinical studies have not yet been completed.

Clinical formulation:

Quantitative composition of the unit formula for the ELOXATIN for Injection

Ingredients	Unit Formula (mg/vial)		
	50 mg Product	100 mg Product	Function
Oxaliplatin	50.00	100.0	Active ingredient
Lactose monohydrate, NF	450.0	900.0	
Water for Injection*, USP	q.s. to 10 mL	q.s. to 20 mL	Solvent
	Not applicable	Not applicable	

*Removed during lyophilization

Route of administration: intravenous infusion

Introduction and drug history:

Oxaliplatin was previously submitted as NDA 21-063. At that time, the non-clinical data was reviewed by Dr. Hua Zheng, with secondary review by Dr. Paul Andrews. No new studies were submitted to NDA 21-492. The non-clinical data in NDA 21-063 was sufficient to support the approval of Eloxatin. The conclusions reached with the review of NDA 21-063 are still valid. The labeling will be reviewed when submitted.

Studies reviewed within this submission: No new studies submitted.

Studies previously reviewed within NDA 21-063 or IND [redacted]

Studies submitted and reviewed for NDA 21-063

I. Pharmacology

Mechanism of Action

Pharmacology Summary (Vol. 1.6, p148) and published reports (Vol.1.10 p221-Vol.1.11, p203)

In Vitro Cytotoxicities

Pharmacology Summary (Vol. 1.6, p148) and published reports (Vol.1.7 p1, Vol.1.8, p1 - Vol.1.9, p45)

In Vivo Antitumor Activities

Pharmacology Summary (Vol. 1.6, p148) and published reports (Vol.1.7 p1, Vol.1.9, p58 - Vol.1.10, p134)

II. Safety Pharmacology

CVR0146 Oxalato Pt DACH and cis Pt: respiratory and cardiovascular actions in anesthetized dogs. (Vol.1.12, p268)

III. Pharmacokinetics and Toxicokinetics

ADME Summary (Vol1.28, p13)

ABS0261 The pharmacokinetics of oxaliplatin (L-OHP) and carboplatin in mice. (Vol.1.28, p46)

ABS0262 Pharmacokinetics of (1R, 2R-diaminocyclohexane) oxaliplatinum (II)[oxaliplatin] in comparison with cisplatin following a single intravenous injection in rabbits. (Vol.1.28, p61)

MIV0250 The *in vitro* biotransformation of [^{3}H]-oxaliplatin in human blood. (Vol.1.28, p189)

MIV0249 The *in vitro* metabolism of [^{3}H]-oxaliplatin in human microsomes. (Vol.1.29, p73)

MET0321 Metabolism of [^{3}H]-oxaliplatin in dog following a single intravenous infusion at 3.6 mg/kg. (Vol.1.28, p70)

EBA0118 Excretion of radioactivity after single intravenous (5 mg/kg) infusion of (3H)-oxaliplatin to the dog. (Vol.1.29, p107)

IV. Toxicology Studies

Single Dose Toxicity Studies
TXA0426 SR96669: A single-dose tolerance study in the rat by oral gavage. (Vol.1.12, p185)

Repeat Dose Toxicity Studies
Toxicology Summary (Vol.1.12, p29) and Summary of the studies previously reviewed

V. Genetic Toxicology Studies *none (all previously reviewed)*

VI. Reproductive and Developmental Toxicology Studies
FER0311 Fertility and reproductive study following sequential intravenous administration in the rat. (Vol.1.19, p26)
TER0307 Teratogenesis trial by intravenous administration in the rat. (Vol.1.20, p208)
TER0308 Teratology study following intravenous administration in the rabbit. (Vol.1.21, p1)

VII. Carcinogenicity Studies *not conducted*

VIII. Special Toxicity Studies
Local Tolerance
TOL1023 Local tolerance at the injection site. (Vol.1.22, p9).
TIP0079 Primary irritation evaluation of SR96669 in rabbits. (Vol.1.22, p21).

Cardiac Toxicity
CVR0147 Study of the effects on the electrocardiogram and the kalemia after a single dose of 200 mg/m^2 by intravenous infusion in non-sedated dogs. (Vol.1.22, p109).
DIV0674 Study of the effects on the electrocardiogram after a single 150 mg/m^2 dose administered by intravenous infusion in non-sedated dogs. (Vol.1.22, p169)
TXA0432 Study of the effects of ondansetron on the acute toxicity of oxaliplatin administered by intravenous infusion at the dose of 200 mg/m^2 in non-sedated dogs. (Vol.1.22, p219)
DIV0627 Single dose intravenous infusion toxicity study of oxaliplatin to assess cardiac effects in Beagle dogs. (Vol.1.24, p1)
DIV0677 Study of cardiac adverse effects after single intravenous infusion in cynomolgus monkeys. (Vol.1.25, p1)

Nephrotoxicity
DIV0678 Comparison of the nephrotoxicity of three platinum derivatives: in vivo experimental approach. (Vol.1.25, p81)
DIV0679 Renal toxicity study via the intravenous route in the rat. (Vol.1.25, p102)

Myelotoxicity
DIV0604 Comparison of the in vitro myelotoxicity of oxaliplatin (SR96669) to cisplatin and carboplatin using human bone marrow stem cells. (Vol.1.25, p165)

Neurotoxicity

Holmes *et al.* (1999) Comparative neurotoxicity of oxaliplatin, cisplatin, and ormaplatin in a Wistar rat model. (Vol.1.25, p174)

Studies previously reviewed by Dr. Schmidt for IND

I. Pharmacology

In Vivo Antitumor Activity

Mathe *et al.* (1985) Antitumor activity of 1-OHP in mice. *Cancer Letters*, 27:135-143

Mathe *et al.* (1989) Oxalatoplatinum of 1-OHP, a third generation platinum complex: an experimental and clinical apprisal and preliminary comparison with cis-platinum and carboplatinum. *Biomed. Pharmacother.*, 43:237-250

Kidani *et al.*, (1976) Examination of antitumor activities of platinum complexes of 1,2-diaminocyclohexane isomers and their related complexes. *Gann*, 67: 921-922

Kidani *et al.*, (1978) Antitumor activities of 1,2-diaminocyclohexane-platinum complexes against sarcoma-180 acites form. *J. Med. Chem.*, 21:1315-1318

Kidani *et al.*, (1978) Antitumor activities of platinum (II) complexes of 1,2-Diaminocyclohexane isomers. *Gann*, 71: 637-643

Noji *et al.*, (1981) Relation of conformation to antitumor activity of platinum (II) complexes of 1,2-cyclohexane-diamine and 2-(aminomethyl)-cyclohexamine isomers against leukemia P388. *J. Med. Chem.* 24:508-515

Vollano *et al.*, (1987) Comparative antitumor activities on platinum(II) and platinum (IV) complexes containing 1, 2-diaminocyclohexane. *J. Med. Chem.*, 30: 716-719

II. Pharmacokinetics and Toxicokinetics

Boughattas *et al.* Report on the pharmacokinetics of 1-OHP in mice. *Debiopharm Int. Rep.* 1991

Boughattas *et al.* Report on the distribution of platinum in the tissues of mice following the administration of 1-OHP: comparison with cisplatin and carboplatin. *Debiopharm Int. Rep.* 1991 (Study Report DIS0288, Vol.1.28, p234)

Pendyala and Creaven *In vitro* protein binding and red blood cell partitioning of oxaliplatin. RPCI Rep. *1990* (Study Report DIS0288, Vol.1.28, p234)

Peytavin Comparative pharmacokinetics study of 3 platinum derivatives: cisplatin, carboplatin and oxaliplatin. *Hospital Paul Brousse Int. Rep.* 1988

Tapiero Pharmacokinetique du trans-1-diamino-cyclohexane oxalatoplatinum (1-OHP): etude preliminare. *Debiopharm Int. Rep.*

III. Toxicology Studies

Acute Toxicity

Corroler *et al.*, (1989) Acute i.v. toxicity in the mouse. Study of lethality. *Rhone-Poulenc Rep.* ST/CRV/TOX 196 (Study Report TXA0427, Vol.1.12 p64)*

D'Alayer *et al.*, (1989) Intravenous acute toxicity in the rat. *T.R.I.S.A. Lab Rep. T922* (Study Report TXA0429, Vol.1.12 p133)

Goadard (1985) Acute toxicity of oxalato DACH-Pt(II) (Oxaliplatin) in mice and rats: Comparison with 1571 RB. *Lab. Roger Bellon Int. Rep. LRB 106/85* (Study Report TXA0428, Vol.1.12 p122)

Roquet & Godard (1985). Oxalato-platinum complex of trans-1-diaminocyclohexane 1-OHP= 1670B. Toxicity study in mice and rats. *Lab. Roger Bellon Inst. Rep. LRB* 318/85 (Study Report TXA0430, Vol.1.12 p217)

Baudet, (1992). Study of the toxicity of oxaliplatin in male rats by i.v. route for 3 days followed by sacrifice on the fifth day. *CERB Study* 910139

Roquet, (1985). Toxicological study of oxalato platinum in dog. *Lab. Roger Bellon Int. rep. LRB 320/85, 1985* (Study Report TXA0431, Vol.1.12 p244)

Repeat Dose Toxicity Studies

Plard *et al.*, (1987). Preliminary toxicological study of 54 780 RP in dogs, administered i.v. in sequential treatment. *Rhone Poulenc Int. Rep. 151* (Study Report DDO0621, Vol.1.15 p263)

Roquet, (1985). Toxicological study of oxalato platinum in dog. *Lab. Roger Bellon Int. rep. LRB 320/85, 1985* (Study Report TXA0431, Vol.1.12 p244)

Baudet, (1992). Study of the comparative toxicity of oxaliplatin and cisplatin, two platinum salts, in male rats by i.v. route for 3 days followed by sacrifice on the fifth day. *CERB Study* 900346 (Study Report DIV0668, Vol.1.13 p1)

D'Alayer *et al.* (1990). Sequenced i.v. toxicity study in the rat (3 cycles of 21 days comprising 5 days of treatment followed by 16 days without treatment). *T.R.I.S.A. Lab. Rep. T928* (Study Report TXC1025, Vol.1.13 p129)

D'Alayer *et al.* (1990). Sequenced i.v. toxicity study in the dog. (3 cycles of 28 days comprising 5 days of treatment followed by 23 days without treatment.) *T.R.I.S.A. Lab. Rep. TP929* (Study Report TXC1026, Vol.1.16 p1)

Roquet,(1985). Toxicological study of oxalato platinum in dog. *Lab. Roger Bellon Int. rep. LRB 320/85, 1985* (Study Report TXA0431, Vol.1.12 p244

D'Alayer *et al.* (1992). 9 week toxicity study in the dog comprising 3 i.v. perfusion at 3 week intervals. *T.R.I.S.A. Lab. Rep. TP995* (Study Report DIV0669, Vol.1.17 p1)

Mathe *et al.* (1992). Repeated dose toxicology study of oxaliplatinum or 1-OHP in baboons. *Hospital Suisse de Paris Int. Rep.* (Study Report TSA1050, Vol.1.19 p1)

IV. Genetic toxicology

Fournier *et al.* (1988). Oxaliplatin-Test of the bone marrow micronucleus in mice by the i.p. route. *Rhone Poulenc Int. Rep.* 200, 1988 (Study Report MUT0091, Vol.1.21 p283)

Marzin (1992) Comparison of the activity of 1-OHP (oxaliplatin) and cisplatin: a study of chromosomal abnormalities by metaphase analysis of human lymphocytes in culture. *Institute pasteur de Lille* (Study Report MAF0034, Vol.1.21 p236)

Marzin (1992) Assay of mutations at the TK locus in L5178Y mouse lymphoma cells by the microtitration technique (resistance to trifluorothymidine), oxaliplatin vs. cisplatin. *Institute pasteur de Lille* (Study Report LYM0041, Vol.1.21 p180)

Thybaud *et al.* (1988) Oxaliplatin (RP 54,780) *in vitro* mutagenicity test. Ames test. *Rhone Poulence Ins. Rep. 176-E* (Study Report HIS1125, Vol.1.21 p157)

V. Reproductive Toxicity Studies *none*

VI. Special Toxicity Studies

D'Alayer *et al.* (1989) Intravenous renal toxicity study in the rat. *T.R.I.S.A. Lab. Rep. T923* (Study Report DIV0679, Vol.1.25 p102)

Roquet and Godard. (1985) Cardiac toxicity of oxaliplatin in rats: Comparison with cisplatin. *Lab. Roger Bellon Int. Rep.* (Study Report DIV0673, Vol.1.22 p88)

Tapiero, (1990) Comparative analysis of the cardiotoxicity of anticancer medication: preliminary studies of trans-1-diaminocyclohexane oxalato platinum (1-OHP). *Debiopharm Int. Rep.* (Study Report DIV0671, Vol.1.22 p59)

DETAILED CONCLUSIONS AND RECOMMENDATIONS:

The non-clinical data submitted in NDA 21492, which is identical to that submitted in NDA21-063, is sufficient to support approval of Eloxatin. The label will be reviewed separately.

/S/

Reviewer signature: _____ /S/

Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wendelyn Schmidt
6/11/02 10:31:41 AM
PHARMACOLOGIST

David Morse
7/22/02 05:43:27 PM
PHARMACOLOGIST

MEMORANDUM

Date: April 7, 2000

4/7/2000

From: Paul A. Andrews, Ph.D.
Pharmacology Team Leader, HFD-150

To: Files for NDA# 21-063

Re: Approvability for Pharmacology and Toxicology
Eloxatin® (oxaliplatin)

Eloxatin is a platinum(II) analog similar to the approved drugs Platinol (cisplatin) and Paraplatin (carboplatin). The DNA adducts formed by oxaliplatin are different than cisplatin and oxaliplatin in that the platinum is bound to the diaminocyclohexane moiety rather than two ammonia ligands. These bulkier DNA adducts may be responsible for the different spectrum of activity of oxaliplatin relative to cisplatin and carboplatin. Sanofi seeks approval of Eloxatin for the first line treatment of advanced colorectal cancer in combination with 5-fluorouracil-based therapy. The extensive pharmacology and toxicology studies submitted to this NDA for Eloxatin have been thoroughly and thoughtfully reviewed by Dr. Hua Zheng. Many of the studies were previously reviewed by Dr. Wendy Schmidt at the time of the original IND and her reviews are included in the package. Dr. Zheng considers the pharmacology and toxicology studies adequate to support approval of the intended indication. I concur with Dr. Zheng's recommendation. The non-clinical studies in the NDA covered the core expectations for cytotoxic drugs in HFD-150. The package included single dose studies in mice (i.v., i.p.), rats (i.v., i.p., oral), dogs (i.v.), and baboons (i.v.); daily x 3 studies in rats; and daily x 5 studies in dogs. Some of these studies included multiple cycles of treatment. These studies support the proposed i.v. administration every two to three weeks. A panel of genetic toxicity studies was submitted. Only the Ames test was negative, but exposure was limited by cytotoxicity at 50 μg/plate. An ICH Stage A fertility study in rats, and Stage C-D developmental toxicity studies in rats and rabbits were submitted. Of particular note, Dr. Zheng used the Draft Pregnancy Risk Integration Guidance to assess the concern for human reproductive and developmental toxicity from oxaliplatin (pp. 23-26 of review). His analysis indicates significant concern for humans for the three positive endpoints of fertility, developmental mortality, and alterations to growth (net adjustments ≥+4). Complete fetal mortality occurred before structural alterations were noted in rats, and in rabbits high enough doses were not administered to consider the study adequate to assess dysmorphogenic potential. Thus, unlike cisplatin and carboplatin, dysmorphogenic findings were not observed with oxaliplatin.

Carcinogenicity studies are not necessary to support approval for the intended indication.

Although the clinical data is not adequate to support approval of this NDA, a detailed labeling review was provided by Dr. Zheng and I agree with the requested changes. AUC data was not used in the label to compare animal exposures associated with critical toxicity endpoints to human exposures because of the extensive biotransformation of oxaliplatin to active forms and because different analytical methods measuring different analytes were used to collect the animal and human pharmacokinetic data.

Recommendations: The pharmacology and toxicology data supports approval of this NDA. There are no outstanding issues.

Original NDA
cc: Div File
HFD-150
/SHirschfeld
/CWilson
/PAndrews

Division of Oncology Drug Products, HFD-150

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

NDA Review #1

NDA No.	21-063	**Type**	NDA	**Date(s) of Submission**	07/22/99
				Received by CDR:	07/23/99

Information to be Conveyed to Sponsor: Yes ( ), No (X)

Reviewer: Hua Zheng, Ph.D.

Date Review Completed: March 30, 2000

Sponsor: Sanofi Pharmaceuticals, Inc.
9 Great Valley Parkway
Malvern, PA 19355

Drug:

Code Name: SR96669, L-OHP, l-OHP, NSC-266046, NSC-271670, JM-83, PR 54780, 1670 RB7

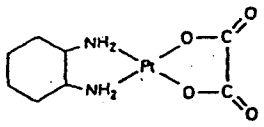
Trade Name: Eloxatin® for Injection (Eloxatine®, Dacplat®)

Generic Name: Oxaliplatin, Oxalatoplatin, Oxalato-platium, DACH-oxalate

Chemical Name: *cis*-[(1*R*,2*R*)-1,2-cyclohexanediamine-*N*,*N*'] [oxalato(2-)-*O*,*O*] platinum 1,2-diaminocyclohexane (DACH)

CAS Number: 61825-94-3

Structure:



Oxaliplatin (l-OHP)

Molecular Formula/ Weight: $C_8H_{14}N_2O_4Pt$ / 397.3

Related INDs/NDAs/DMFs: IND [redacted]

Class: Platinum derivative

Proposed Indication: First-line treatment of advanced colorectal cancer in combination with 5-FU-based therapy

Clinical Formulation: The commercial products are supplied as two dose vial, 50 mg and 100 mg of ELOXATIN® for Injection are the sterile, lyophilized powder contained in 30 mL, or 50 mL clear glass vials.

Quantitative composition of the unit formula for the ELOXATIN for Injection

Ingredients	Unit Formula (mg/vial)		
	50 mg Product	100 mg Product	Function
Oxaliplatin	50.00	100.0	Active ingredient
Lactose monohydrate, NF	450.0	900.0	
Water for Injection*, USP	q.s. to 10 mL	q.s. to 20 mL	Solvent
	Not applicable	Not applicable	

*Removed during lyophilization

Route of Administration: Intravenous Infusion

Proposed Dose: Administration of 85 mg/m^2 every two weeks or 125 mg/m^2 every three weeks, in combination with 5-FU-based therapy

Previous Review(s), Date(s), and Reviewer(s):

IND [redacted]	Safety Review	W. J. Schmidt	04/01/93
IND [redacted]	Original Review	W. J. Schmidt	04/13/93

Studies submitted and reviewed for this NDA

I. Pharmacology

Mechanism of Action

Pharmacology Summary (Vol. 1.6, p148) and published reports (Vol.1.10 p221-Vol.1.11, p203)

In Vitro Cytotoxicities

Pharmacology Summary (Vol. 1.6, p148) and published reports (Vol.1.7 p1, Vol.1.8, p1 -Vol.1.9, p45)

In Vivo Antitumor Activities

Pharmacology Summary (Vol. 1.6, p148) and published reports (Vol.1.7 p1, Vol.1.9, p58 -Vol.1.10, p134)

II. Safety Pharmacology

CVR0146 Oxalato Pt DACH and cis Pt: respiratory and cardiovascular actions in anesthetized dogs. (Vol.1.12, p268)

III. Pharmacokinetics and Toxicokinetics

ADME Summary (Vol1.28, p13)

ABS0261 The pharmacokinetics of oxaliplatin (L-OHP) and carboplatin in mice. (Vol.1.28, p46)

ABS0262 Pharmacokinetics of (1R, 2R-diaminocyclohexane) oxaliplatinum (II)[oxaliplatin] in comparison with cisplatin following a single intravenous injection in rabbits. (Vol.1.28, p61)

MIV0250 The *in vitro* biotransformation of [^{3}H]-oxaliplatin in human blood. (Vol.1.28, p189)

MIV0249 The *in vitro* metabolism of [^{3}H]-oxaliplatin in human microsomes. (Vol.1.29, p73)

MET0321 Metabolism of [^{3}H]-oxaliplatin in dog following a single intravenous infusion at 3.6 mg/kg. (Vol.1.28, p70)

EBA0118 Excretion of radioactivity after single intravenous (5 mg/kg) infusion of (3H)-oxaliplatin to the dog. (Vol.1.29, p107)

IV. Toxicology Studies

Single Dose Toxicity Studies

TXA0426 SR96669: A single-dose tolerance study in the rat by oral gavage. (Vol.1.12, p185)

Repeat Dose Toxicity Studies

Toxicology Summary (Vol.1.12, p29) and Summary of the studies previously reviewed

V. Genetic Toxicology Studies *none (all previously reviewed)*

VI. Reproductive and Developmental Toxicology Studies

FER0311 Fertility and reproductive study following sequential intravenous administration in the rat. (Vol.1.19, p26)

TER0307 Teratogenesis trial by intravenous administration in the rat. (Vol.1.20, p208)

TER0308 Teratology study following intravenous administration in the rabbit. (Vol.1.21, p1)

VII. Carcinogenicity Studies *not conducted*

VIII. Special Toxicity Studies

Local Tolerance

TOL1023 Local tolerance at the injection site. (Vol.1.22, p9).

TIP0079 Primary irritation evaluation of SR96669 in rabbits. (Vol.1.22, p21).

Cardiac Toxicity

CVR0147 Study of the effects on the electrocardiogram and the kalemia after a single dose of 200 mg/m^2 by intravenous infusion in non-sedated dogs. (Vol.1.22, p109).

DIV0674 Study of the effects on the electrocardiogram after a single 150 mg/m^2 dose administered by intravenous infusion in non-sedated dogs. (Vol.1.22, p169)

TXA0432 Study of the effects of ondansetron on the acute toxicity of oxaliplatin administered by intravenous infusion at the dose of 200 mg/m^2 in non-sedated dogs. (Vol.1.22, p219)

DIV0627 Single dose intravenous infusion toxicity study of oxaliplatin to assess cardiac effects in Beagle dogs. (Vol.1.24, p1)

DIV0677 Study of cardiac adverse effects after single intravenous infusion in cynomolgus monkeys. (Vol.1.25, p1)

Nephrotoxicity

DIV0678 Comparison of the nephrotoxicity of three platinum derivatives: in vivo experimental approach. (Vol.1.25, p81)

DIV0679 Renal toxicity study via the intravenous route in the rat. (Vol.1.25, p102)

Myelotoxicity

DIV0604 Comparison of the in vitro myelotoxicity of oxaliplatin (SR96669) to cisplatin and carboplatin using human bone marrow stem cells. (Vol.1.25, p165)

Neurotoxicity

Holmes *et al.* (1999) Comparative neurotoxicity of oxaliplatin, cisplatin, and ormaplatin in a Wistar rat model. (Vol.1.25, p174)

Studies previously reviewed by Dr. Schmidt for IND [redacted]

I. Pharmacology

In Vivo Antitumor Activity

Mathe *et al.* (1985) Antitumor activity of 1-OHP in mice. *Cancer Letters*, 27:135-143

Mathe *et al.* (1989) Oxalatoplatinum of 1-OHP, a third generation platinum complex: an experimental and clincial apprisal and prelimimary comparison with cis-platinum and carboplatinum. *Biomed. Pharmacother.*, 43:237-250

Kidani *et al.*, (1976) Examination of antitumor activities of platinum complexes of 1,2-diaminocyclohexane isomers and their related complexes. *Gann*, 67: 921-922

Kidani *et al.*, (1978) Antitumor activities of 1,2-diaminocyclohexane-platinum complexes against sarcoma-180 acitis form. *J. Med. Chem.*, 21:1315-1318

Kidani *et al.*, (1978) Antitumor activities of platinum (II) complexes of 1,2-Diaminocyclohexane isomers. *Gann*, 71: 637-643

Noji *et al.*, (1981) Relation of conformation to antitumor activity of platinum (II) complexes of 1,2-cyclohexane-diamine and 2-(aminomethyl)-cyclohexamine isomers against leukemia P388. *J. Med. Chem.* 24:508-515

Vollano *et al.*, (1987) Comparative antitumor activities on platinum(II) and platinum (IV) complexes containing 1, 2-diaminocyclohexane. *J. Med. Chem.*, 30: 716-719

II. Pharmacokinetics and Toxicokinetics

Boughattas *et al.* Report on the pharmacokinetics of 1-OHP in mice. *Debiopharm Int. Rep.* 1991

Boughattas *et al.* Report on the distribution of platinum in the tissues of mice following the administration of 1-OHP: comparison with cisplatin and carboplatin. *Debiopharm Int. Rep.* 1991 (Study Report DIS0288, Vol.1.28, p234)

Pendyala and Creaven *In vitro* protein binding and red blood cell partitioning of oxaliplatin. RPCI Rep. *1990* (Study Report DIS0288, Vol.1.28, p234)

Peytavin Comparative pharmacokinetics study of 3 platinum derivatives: cisplatin, carboplatin and oxaliplatin. *Hospital Paul Brousse Int. Rep.* 1988

Tapiero Pharmacokinetique du trans-1-diamino-cyclohexane oxalatoplatinum (1-OHP): etude preliminare. *Debiopharm Int. Rep.*

III. Toxicology Studies

Acute Toxicity

Corroler *et al.*, (1989) Acute i.v. toxicity in the mouse. Study of lethality. *Rhone-Poulenc Rep.* ST/CRV/TOX 196 (Study Report TXA0427, Vol.1.12 p64)*

D'Alayer *et al.*, (1989) Intravenous acute toxicity in the rat. *T.R.I.S.A. Lab Rep. T922* (Study Report TXA0429, Vol.1.12 p133)

Goadard (1985) Acute toxicity of oxalato DACH-Pt(II) (Oxaliplatin) in mice and rats: Comparison with 1571 RB. *Lab. Roger Bellon Int. Rep. LRB 106/85* (Study Report TXA0428, Vol.1.12 p122)

Roquet & Godard (1985). Oxalato-platinum complex of trans-1-diaminocyclohexane 1-OHP= 1670B. Toxicity study in mice and rats. *Lab. Roger Bellon Inst. Rep. LRB* 318/85 (Study Report TXA0430, Vol.1.12 p217)

Baudet, (1992). Study of the toxicity of oxaliplatin in male rats by i.v. route for 3 days followed by sacrifice on the fifth day. *CERB Study* 910139

Roquet, (1985). Toxicological study of oxalato platinum in dog. *Lab. Roger Bellon Int. rep. LRB 320/85, 1985* (Study Report TXA0431, Vol.1.12 p244)

Repeat Dose Toxicity Studies

Plard *et al.*, (1987). Preliminary toxicological study of 54 780 RP in dogs, administered i.v. in sequential treatment. *Rhone Poulenc Int. Rep. 151* (Study Report DDO0621, Vol.1.15 p263)

Roquet, (1985). Toxicological study of oxalato platinum in dog. *Lab. Roger Bellon Int. rep. LRB 320/85, 1985* (Study Report TXA0431, Vol.1.12 p244)

Baudet, (1992). Study of the comparative toxicity of oxaliplatin and cisplatin, two platinum salts, in male rats by i.v. route for 3 days followed by sacrifice on the fifth day. *CERB Study* 900346 (Study Report DIV0668, Vol.1.13 p1)

D'Alayer *et al.* (1990). Sequenced i.v. toxicity study in the rat (3 cycles of 21 days comprising 5 days of treatment followed by 16 days without treatment). *T.R.I.S.A. Lab. Rep. T928* (Study Report TXC1025, Vol.1.13 p129)

D'Alayer *et al.* (1990). Sequenced i.v. toxicity study in the dog. (3 cycles of 28 days comprising 5 days of treatment followed by 23 days without treatment.) *T.R.I.S.A. Lab. Rep. TP929* (Study Report TXC1026, Vol.1.16 p1)

Roquet, (1985). Toxicological study of oxalato platinum in dog. *Lab. Roger Bellon Int. rep. LRB 320/85, 1985* (Study Report TXA0431, Vol.1.12 p244)

D'Alayer *et al.* (1992). 9 week toxicity study in the dog comprising 3 i.v. perfusion at 3 week intervals. *T.R.I.S.A. Lab. Rep. TP995* (Study Report DIV0669, Vol.1.17 p1)

Mathe *et al.* (1992). Repeated dose toxicology study of oxaliplatinum or 1-OHP in baboons. *Hospital Suisse de Paris Int. Rep.* (Study Report TSA1050, Vol.1.19 p1)

IV. Genetic toxicology

Fournier *et al.* (1988). Oxaliplatin-Test of the bone marrow micronucleus in mice by the i.p. route. *Rhone Poulenc Int. Rep.* 200, 1988 (Study Report MUT0091, Vol.1.21 p283)

Marzin (1992) Comparison of the activity of 1-OHP (oxaliplatin) and cisplatin: a study of chromosomal abnormalities by metaphase analysis of human lymphocytes in culture. *Institute pasteur de Lille* (Study Report MAF0034, Vol.1.21 p236)

Marzin (1992) Assay of mutations at the TK locus in L5178Y mouse lymphoma cells by the microtitation technique (resistance to trifluorothymidine), oxaliplatin vs. cisplatin. *Institute pasteur de Lille* (Study Report LYM0041, Vol.1.21 p180)

Thybaud *et al.* (1988) Oxaliplatine (RP 54,780) *in vitro* mutagenicity test. Ames test. *Rhone Poulence Ins. Rep. 176-E* (Study Report HIS1125, Vol.1.21 p157)

V. Reproductive Toxicity Studies *none*

VI. Special Toxicity Studies

D'Alayer *et al.* (1989). Intravenous renal toxicity study in the rat. *T.R.I.S.A. Lab. Rep. T923* (Study Report DIV0679, Vol.1.25 p102)

Roquet and Godard. (1985) Cardiac toxicity of oxaliplatin in rats: Comparison with cisplatin. *Lab. Roger Bellon Int. Rep.* (Study Report DIV0673, Vol.1.22 p88)

Tapiero, (1990) Comparative analysis of the cardiotoxicity of anticancer medication: preliminary studies of trans-1-diaminocyclohexane oxalato platinum (1-OHP). *Debiopharm Int. Rep.* (Study Report DIV0671, Vol.1.22 p59)

Note that portions of this review were excerpted directly from the sponsor's submission.

Review

Introduction and Drug History: This is the pharmacology/toxicology review for an NDA submitted for marketing approval of ELOXATIN® for the first-line treatment of advanced colorectal cancer in combination with 5-FU-based therapy.

ELOXATIN® ([SP-4-2-(1*R-trans*)] - (1,2-cyclohexanediamine-*N,N'*) [ethanedioato (2-) - *0,0'*] platinum), also known as Eloxatine®, Decaplat®, oxaliplatin, oxalatoplatin, oxalatoplatinum, DACH, DACH-oxalate, SR96669, PR-54780, 1670 RB7, 1-OHP, L-OHP, *l*-OHP, NSC-2666046, NSC-271670, or JM-83, is a novel antineoplastic platinum (Pt) containing compound complexed to 1,2-diaminocyclohexane (DACH) in the *trans-R,R* or *l* confirmation and with an oxalate ligand as a leaving group.

Oxaliplatin was originally developed by Roger Bellon (France), a subsidiary of Rhône-Poulenc Rorer. Subsequently, Sanofi licensed oxaliplatin in France and other countries. ELOXATINE® has been marketed in France since April 1996 as second-line therapy for the treatment of advanced colorectal cancer in combination with fluoropyrimidines. In 1998, oxaliplatin was also approved in France for first-line therapy in combination with 5-fluorouracil (5-FU) and folinic acid (FA) or as a single agent when patients are not candidates for 5-FU therapy. ELOXATIN® was developed for US marketing under IND [redacted]

I. Pharmacology

The pharmacology section of this review will summarize the major *in vitro* and *in vivo* findings regarding the antitumor activity of oxaliplatin.

Oxaliplatin demonstrates broad spectrum *in vitro* cytotoxic or antiproliferative activity against a variety of murine and human tumor cell lines. Oxaliplatin is more active in ~40% of cell lines compared to cisplatin. In general, the cytotoxic and antitumor activity of oxaliplatin is equal or superior to that observed for cisplatin. In an *in vitro* human tumor cloning assay, oxaliplatin and cisplatin had similar activity against several types of human tumors obtained directly from patients. Oxaliplatin also demonstrates *in vitro* cytotoxic and *in vivo* antitumor activity (including curative activity) in several cell lines / tumor models that are resistant to cisplatin. Oxaliplatin was shown to have additive and/or synergistic cytotoxic and antitumor activity in combination with a variety of standard antineoplastic agents, including 5-fluorouracil, SN-38, gemcitabine, or cisplatin.

Oxaliplatin as a single agent demonstrated *in vivo* antitumor activity against a variety of murine tumor models and human xenograft model in athymic mice. Oxaliplatin was more active than cisplatin in the following murine tumors: L1210 leukemia, LGC lymphoma, and MA-16c mammary tumors.

Table 1. In vitro tumor cytotoxicity of oxaliplatin as single agent

Tumor Cell Lines	Assay Method	Drug Conc. (μM)	Duration of Exposure	Results IC_{50} (μM) [a]		Report No. *(Vol/Pg)*
				Oxaliplatin	*Cisplatin*	
Murine leukemia						
L1210	Cell Counting	0.5 – 500	1 h	1.8	0.9	P38 Vol 1.8/Pg77
L1210 /DDP (cisplatin resistant)				1.8	70	
L1210PtR4 (cisplatin resistant)	Cell Counting	Unknown	72 h	0.11	10.8	P6 Vol 1.8/Pg1
L1210DDP5 (cisplatin resistant)				0.22	20.6	
L1210	Cell Counting	Unknown	24 h	0.35	0.33	P39 Vol 1.8/Pg91
L1210 -resistant (cisplatin resistant)				0.8	15	
P388	Cell Counting	Unknown	72 h	0.97	0.67	P6 Vol 1.8/Pg1
P388PtR4 (cisplatin resistant)				17.1	16.2	
P388	Cell Counting	0.5 – 50	1 h	3.0	1.0	P38 Vol 1.8/Pg77
P388/DDP (cisplatin resistant)				12.5	8.5	
Human - Colon						
HT-29	Cell Counting	Unknown	15-120 min.	0.7		P42; Vol1.8/Pg148
HT-29		Unknown	30 min.	25.4		P35, Vol 1.8/Pg129
HT-29		0.1 - 100	48 h	2.1	6.7	P5 Vol1.9/Pg160
CaCo2				2.8	14.9	
HEC59	Colony formation	0 - 50	1 h	5.9	14.0	P41, Vol1.8/Pg121
Human - Ovarian						
A2780	SRB Colorimetric	0.1- 1000	48 h	0.17	0.76	P8 Vol 1.8/Pg17
A2780/CP (cisplatin resistant)				0.39	13.8	
A2780 (1A9)	SRB microculture colorimetric	Unknown	4 days	0.12	0.21	P10 Vol 1.8/Pg37
A2780E (80) (cisplatin resistant)				0.56	19.3	
A2780 / DDP (cisplatin resistant)		0.1 – 100	48 h	7.9	7.5	P5 Vol1.9/Pg160
OVCAR-3		Unknown	48 h	25	4.5	P9 Vol 1.8/Pg26
2008		0.1 – 100	48 h	10	1.9	P5 Vol1.9/Pg160
2008 C13 (cisplatin resistant)				13.5	13.1	

Tumor Cell Lines	Assay Method	Conc. (μM)	Exposure Time	Results (IC_{50}) [a]		Report No. (Vol/Pg)
Human - Ovarian				*Oxaliplatin*	*Cisplatin*	
41M	SRB Colorimetric Assay	0.1 - 100	48 h	3.64	6.03	P22 Vol 1.8/Pg62
41M-cisR				0.51	0.90	
CH1				13.6		
CH1-cisR						
SKOV-3						
Human - Breast						
MCF-7	Colorimetric Assay	Unknown	15-120 min.	0.3	4.2	P42 Vol1.8/Pg148
MCF-7	Colorimetric Assay	0.1 -100	48 h	7.45	14.5	P5 Vol1.9/Pg160
MCF-7mdr (multidrug resist.)				12.2	9.2	
MDA-MB231				17.9	5.6	
Human - Melanoma						
HT-144	Cell Counting	0.1 - 100	48 h	12.2	9.2	P8 Vol 1.8/Pg91
SK-MEL-2				17.9	5.6	
Human - Bladder						
RT4	Cell Counting	0.1 - 1000	48 h	11.1	12.3	P8 Vol 1.8/Pg91
TCC				15.0	3.7	
Human - Glioma						
U-87MG	Cell Counting	0.1 - 1000	48 h	17.6	14.4	P8 Vol 1.8/Pg91
U-373 MG				2.95	11.4	
Human - Erythroleukemia						
K562	Colony Formation	unknown	15-120 min.	0.4	1.8	P42 Vol1.8/Pg148
Human – HeLa						
KB3-1	SRB Assay	unknown	96 h	0.39	0.75	P10 Vol 1.8/Pg40
KBCP (20) (cisplatin resistant)				1.05	58.5	
Human – Non Small Cell Lung						
PC-9	Colony Formation Assay	unknown	10 days	2.6	0.6	P7 Vol 1.8/Pg8
PC-9/CDDP (cisplatin resistant)				13.3	11.0	
PC-14				6.1	2.7	
PC-14/CDDP (cisplatin resistant)				14.3	20.8	
Human – Squamous Cell Lung						
SW 1573	Colony Formation	0.1 - 100	1 h	12	15	P43, Vol 1.8 /Pg149
Human – Neuorblastoma						
LAN-1	Colony Formation	0.05 - 40	12, 24, or 48 h data: 24 h	0.46	0.58	P40 Vol 1.8/Pg 118
BE(2)M-17				0.43	0.34	
SK-N-DZ				1.03	0.46	
Human – Non-seminomatous germ cell tumor						
1777NRp CL-A	SRB Colorimetric Assay	0.01 – 100 mM	2, 24 & 96 h (data: 24 h)	1.0	2.6	P44 Vol1.8/Pg158
1411HP (high CDDP resistance)				15	12	

[a] IC_{50} = the concentration at which the growth of the cultured cells was inhibited by 50% of that of control

***In vivo* Antitumor Studies for of oxaliplatin as a single agent against Murine tumors**

#s per group	Tx Schedule (days)	Route	Dose (mg/m^2)	Results & interpretations (%T/C, survivors)	Report No. (Vol/Pg)
Leukemia L1210 (murine tumor implanted IP)					
6 or 10	1, 5, 9	IP	9.36 – 37.5	At 18.75 - 37.5 mg/m^2: %T/C = 308-380 3-5/6 survivors	P23, P59, Vol 1.9/ Pg58, 135 P38, Vol 1.8/Pg77
8	1, 5, 9, 13	IP, IV	3 - 36	At 18 mg/m^2: %T/C = 245 (i.p), 140 (i.v.)	P59 Vol 1.9/Pg160
≥ 5	1, 5, 9, 13	IP	2.4 - 120	%T/C = 167 – 419 4/6 survivors	P60,Vol 1.9/Pg141 P39, Vol 1.8/Pg91
6	5, 9, 13	IP	18.78 - 75	At 37.5 mg/m^2: %T/C = 320 3/6 survivors (> 60 days)	P59 Vol 1.9/Pg135
≥ 5	1 or qd 1-9	IP	single: 30, 36 qd: 4.8	Single dose: %T/C = 179 At qd (1-9) 4.8 mg/m^2: %T/C = 178	P25 Vol 1.9/Pg76
Leukemia L1210/DDP (murine tumor implanted IP, CDDP resistant model)					
6 & 10	1, 5, 9	IP	4.68 – 19.75	At 18.75 mg/m^2: %T/C = 308 - 726 6/6 survivors	P38, Vol 1.8/Pg77 P59, Vol 1.9/Pg135
≥ 5	1, 5, 9, 13	IP	2.85 – 22.5	At 22.5 -30 mg/m^2: %T/C = 177	P60, Vol 1.9/Pg141 P39, Vol 1.8/Pg91
Leukemia P388 (murine tumor implanted IP)					
6 & 10	1, 5, 9	IP	4.68 – 37.5	At 37.5 mg/m^2: %T/C = 221-210	P59, Vol 1.9/Pg135 P38, Vol 1.8/Pg77
10	1, 5, 9	IP	12 - 45	%T/C = 220-283	P65, Vol 1.9/Pg 207
6 & 10	1, 5	IP	4.68 -300	At 18.75 - 37.5 mg/m^2: %T/C = 188 - 231	P26, 27, 28 & 29 Vol 1.9/Pg82, 97, 100 & 110
Leukemia L40AkR (murine tumor implanted IP)					
unknown	1, 5, 9	IV	15-22.5	At 22.5 mg/m^2: %T/C = 177	P63, Vol 1.9/Pg190
Lymphoma LGC (murine tumor implanted IP)					
unknown	1, 5, 9	IV	15-22.5	At 15 mg/m^2: > 50% mice cured	P63, Vol 1.9/Pg190
Colon C26, C38 (murine tumor implanted IP, SC)					
6 & 10	1, 5 2, 9	IP	9.36 – 37.5 15 - 60	C26: at 37.5 mg/m^2: %T/C = 143 C38: at 30 mg/m^2: %T/C = 153	P38, Vol 1.8/Pg77
Lung Lewis (murine tumor implanted SC)					
6 & 10	q2d × 10	IP	3.75 - 15	3.75- 7.5 mg/m^2: %T/C = 145 -159	P38, Vol 1.8/Pg77 P59 Vol 1.9/Pg135
Mammary MA-16c (murine tumor implanted SC)					
6 & 10	1, 5, 9	IP	15 – 22.5	22.5 mg/m^2: %T/C = 206 > 43% cured	P63, Vol 1.9/Pg190
Melanoma B16 (murine tumor implanted IP)					
6 & 7	1, 5, 9	IP	3.73 – 30	15 - 30 mg/m^2: %T/C = 128 - 200 1/6 survivors (30 mg/m^2)	P38, Vol 1.8/Pg77 P59, Vol 1.9/Pg135
10	qd 1- 9	IP	4.8 -9	%T/C = 171-178	P25, Vol 1.9/Pg76 P58 Vol 1.9/Pg121
Sarcoma M5076 (murine tumor implanted IP, SC)					
6 - 10	1, 5, 9 1, 5, 9, 13, 18 8, 12, 16	IP	0.93 - 30	30 mg/m^2: %T/C = 155-187(SC) %T/C = 358 (IP) 7.5 mg/m^2: %T/C = 280 4/6 survivors 30 mg/m^2: %T/C = 358	P38, Vol 1.8/Pg77 P59, Vol 1.9/Pg135
Sarcoma 180 (murine tumor implanted IP)					
6	1, 5, 9	IP	3.73 – 30	9 mg/m^2: TGI* = 91%	P30, Vol 1.9/Pg115
Mammary GR (murine tumor implanted SC)					
6	4 or 4, 6, 10	IP	30	30 mg/m^2: TGI* = 46%	P5

TGI = tumor growth inhibition; 100% - (the mean tumor weight of treated mice divided by the mean tumor weight of non-treated)

***In vivo* antitumor activity of oxaliplatin in human xenograft (SC) models in athymic mice**

#s per grp	Tx Schedule (days)	Route	Dose (mg/m²)	Results & interpretations (%T/C, survivors)	Report No. (Vol/Pg)
Colon HT-29, DLD-2 (human xenograft implanted SC)					
≥ 6	13, or 13, 16	IP	30	Single injection: no effect Repeat dose: significant tumor inhibition	P5
8-10	1	IP	22.5 – 45	At 45 mg/m²: TGI = 20% (HT-29) TGI = 51% (DLD-2)	P65, Vol 1.9/pg251
10	qd × 5	IP	7.5 – 15	At 15 mg/m²: TGI = 38%	P64, Vol 1.9/pg207
Lung SK-MES (human xenograft implanted SC)					
10	1	IP	22.5 – 45	At 45 mg/m²: TGI = 58%	P66, Vol 1.10/pg1
10	qd × 5	IP	7.5 – 15	At 15 mg/m²: TGI = 30%	P66, Vol 1.10/pg1
Lung MV-522 (human xenograft implanted SC)					
8	1	IP	22.5 – 45	At 22.5 mg/m²: TGI = 10%	P67, Vol 1.9/pg251
8 – 10	1	IP	22.5 – 45	At 45 mg/m²: TGI = 31%	P65, Vol 1.9/pg251
8	qd × 5	IP	22.5 – 45	At 45 mg/m²: TGI = 1.8%	P68, Vol 1.10/pg55
10	qd × 5	IP	22.5 – 45	At 15 mg/m²: TGI = 35%	P64, Vol 1.9/pg207
Mammary MX-1 (human xenograft implanted SC)					
6	1	IP	37.5	At 12.5 mg/m²: TGI = 82%	P59, Vol 1.9/pg135

TGI = Tumor growth inhibition; 100% - (the mean tumor weight of treated mice divided by the mean tumor weight of non-treated)

II. Safety Pharmacology

CVR0146 Oxalato Pt DACH and cis Pt: Respiratory and cardiovascular actions in anesthetized dogs. (Vol.1.12, p268). Conducted by Laboratoire Roger Bellon of Sanofi. The study was completed at Dec. 20, 1984 as a GLP study. Dated signature sheet for GLP and QA compliance was not provided. Oxaliplatin (Protocol #2), at 300 mg/m² but not 180 mg/m²: 1) lowered the blood pH levels, indicating metabolic acidosis; 2) caused systemic hypotension when administered to the dogs anesthetized with barbiturates.

Test substance: oxaliplatin (Japanese product), 0.15% test article in 0.9% NaCl
Route of administration: i.v. infusion via left cephalic vein
Evaluation Method:
Respiration: Rate and ventilation/min, compliance and pulmonary resistance
Cardiovascular: HR, left ventricular pressure and right ventricular power change rate, sub-sigmoid arterial pressure, pulmonary arterial pressure, and right arterial pressure

Protocol No.	***1***	***2***	***3***
number/sex/group	1	1 ♂	1 ♂
Treatment	Oxali or CDDP	Oxali or CDDP	
Dose (mg/m²)	272 mg/m² and 128 mg/m² 2.5 h later	300	52 mg/m² and 128 mg/m² 2.5 h later
Result	Acidosis, low respiration rate, pulmonary and systemic arterial hypertension, respiration arrest and death (♀)	↓ aortic pressure ↓ blood pH	no symptoms observed

III. ADME and Pharmacokinetics/Toxicokinetics

ADME Summary (Vol 8.28, p13)

ABS0261 The pharmacokinetics of oxaliplatin (L-OHP) and carboplatin in mice. (Vol.1.28, p46)

ABS0262 Pharmacokinetics of (1R, 2R-diaminocyclohexane) oxaliplatinum (II)[oxaliplatin] in comparison with cisplatin following a single intravenous injection in rabbits. (Vol.1.28, p61)

MIV0250 The *in vitro* biotransformation of [^{3}H]-oxaliplatin in human blood. (Vol.1.28, p189)

MIV0249 The *in vitro* metabolism of [^{3}H]-oxaliplatin in human microsomes. (Vol.1.29, p73)

MET0321 Metabolism of [^{3}H]-oxaliplatin in dog following a single intravenous infusion at 3.6 mg/kg. (Vol.1.28, p70)

EBA0118 Excretion of radioactivity after single intravenous (5 mg/kg) infusion of (^{3}H)-oxaliplatin to the dog. (Vol.1.29, p107)

Summary of ADME and PK/TK

The pharmacokinetics of oxaliplatin after single dose IV administration were investigated in mice and dogs as summarized in the follow table.

Summary of PK-TK Parameters after Single Dose of Oxaliplatin Dosing

Species (#of animals)	Route & Schedule	Dose (mg/m^2)	AUC $_{0-\infty}$ (µg•hr/mL)	Cmax (µg/ml)	T1/2 β (hr)	Report Number GLP
Mice (324 ♂)[a]	IV bolus, single dose	51	PUF: 11,760 (196 mg•min/L)	Bl: 12.5 Pl: 15.6 PUF: 12.2	0.82	ABS0261 GLP: No
Dogs (4 ♂) [b]	IV infusion (1.5 h), single dose	72 ^{3}H-DACH	Bl [e]: 108 µg eq.•h/g Pl [f]: 151 µg eq.•h/g PUF g: 12.4 µg eq.•h/g	Bl: 1.67 µg eq/g Pl: 2.84 µg eq/g BUF: 1.33 µg eq/g	Bl: 119 Pl: 119 PUF: 70	MET0321 GLP & QA: Yes
Dogs (4/sex) [c]	IV infusion (2 h), single dose	134-190	Pl: 122 - 207 Bl: 104 -132 PUF: 5 – 14 (0-24)	Plasma: 2.7 - 6.6 Blood: 1.5 – 2.8 PUF: 1.45 - 3.82	Pl: 100 Bl: 115 PUF: 7	DIV0626 GLP & QA: Yes
Dogs (5/sex) [d]	IV infusion (2 h), single dose	150, 200	Pl: 169, 211 Bl: 91, 128 PUF: 12, 14	Pl: 3.44, 6.0 Bl: 1.5, 2.6 PUF: 1.95, 3.11	Pl: 115 Bl: 125 PUF: 24	DIV0627 GLP & QA: Yes

[a] Analytical method: platinum concentrations determined by flameless atomic absorption spectrophotometry; [b] Analytical method: radioactivity assay by [redacted] and urine by [redacted] Analytical method: platinum concentrations by a exploratory ICP-MS assay; [d] Analytical method: platinum concentrations by a validated ICP-MS assay; [e] Pl: Plasma; [f] Bl: Blood; g Plasma ultrafiltrate

Species /Study No.	Mice ABS0261	Dogs MET0321	Dogs DIV0626	Dogs DIV0627
AUC/Dose (mg/m^2)	PUF: 230	Pl: 1.5 Bl: 2.1 PUF: 0.17	Pl: 0.9 - 1.2 Bl: 0.5 - 0.7 PUF: 0.07	Pl: 1.06 - 1.13 Bl: 0.61- 0.64 PUF: 0.07-0.08

The half-lives were consistent in the plasma and whole blood fraction in dogs (10-120 hrs) while in mice t½ β was only 49 minutes. Systemic exposure after single exposure was 1353-2875 fold higher in mice than in dogs when normalized to the dose (body surface area). However, this huge difference was mostly likely due to the different assay methods used in determining the oxaliplatin concentrations. It is noted that in the mice, the total platinum was measured using FAA and in the dog, more specific assay were employed. Among dogs in 3 different GLP studies, the systemic exposure (AUC) were quite consistent with the dose. In the toxicokinetic studies in dogs (dose range finding study: DIV0626, and the definitive study: DIV0627), platinum levels in the plasma ultrafiltrate peaked in most animals at the end

of the 2 hr infusion, and then declined bi-phasically with an elimination half life of ~24 h. Higher platinum levels were detected in blood and plasma than in ultrafiltrate, both declining more slowly with similar half-lives (mean t ½ = 112-129 h). These results are consistent with data from a radiolabel study in dogs (MET0321) and indicate that oxaliplatin and its biotransformation products are primarily bound to plasma proteins.

Protein Binding: *In vitro*, the oxaliplatin serum binding was time dependent and covalent. Oxaliplatin was 85-88% bound to plasma protein over a 5 h period. The binding of total platinum in the whole blood to RBC was rapid, reaching equilibrium by 4 h. At this time (4-5 hrs), 37-53% of total platinum was found in RBCs. Of the oxaliplatin bound to RBCs, 12% was bound to the membrane, 31% to the cytosolic proteins and 12% was ultrafiltrable. In conclusion, a significant proportion of platinum is bound to plasma and/or cellular proteins.

Tissue Distribution Tissue distribution profile are summarized in the following table. Extensive tissue distribution of platinum was observed in all tissues in both mice and rabbits. The IP study (DIS0829) actually determined the distribution of platinum from a mixture of the dichloro DACH platin and oxalipatin and therefore the results are difficult to interpret. The highest platinum levels from oxaliplatin were detected in the kidney and spleen in both mice and rabbits.

Species (# animals)	Route & Schedule	Dose (mg/m^2)	Results and Intepretations	Report No. GLP
Mice (134 ♂)	IV bolus, single dose	51	• Platinum concentration were found in large number of tissues 24 h postdose • Highest concentration in spleen and kidney	DIS0288 GLP: No
Rats (♂, # not specified)	IP, single or two doses	40	• Highest tissue levels in kidneys	DIS0829 GLP: No
Rabbits (18 ♂) 3/time point)	Single IV Infusion, 1.5 h	44	• Highest platinum levels in kidney (31-45%), spleen (13-17%) and liver (9-11%) on D1, 3 and 5 post-dose[a]	ABS0262 GLP: No

[a] % of the total measurable tissue levels in ppm

Metabolism: The *in vitro* biotransformation of ^{3}H-oxaliplatin after incubation in whole blood and plasma were determined in plasma ultrafiltrate samples and are summarized in the following table.

In vivo studies with ^{3}H-oxaliplatin underwent rapid non-enzymatic biotransformation after IV administration. The major products found in the plasma ultrafiltrate of rats included dichloro DACH platin, $(cystein)_2$ DACH platin, glutathione DACH platin, $(glutathione)_2$ DACH platin, methionine DACH platin and free DACH. Similar biotransformation products were seen in humans following a single IV infusion (130 mg/m^2) to cancer patients (PKM2983).

I. Biotransformation of Oxaliplatin *in vitro*

Type of Study (Concentration)	Biological Samples	Tx Duration	Results	Report Number GLP
Rat Biotransformation (20 µg/ml)	Bl, Pl, PUF from ♂ rat	Blood incubated with ^{3}H-Oxaliplatin, samples taken various intervals up to 24 h	• 3 major products in PUF: free oxaliplatin and cystein- methionine conjugates	Literature GLP: No
Dog-*in vitro* Stability (25 - 500 µg/ml)	Bl, Pl, PUF from ♂ dog	Storage for 0, 0.5 and 2 h at 4°C and RT, PUF at -80°C for 28 days	• ^{3}H oxaliplatin was unstable in blood, plasma ultrafiltrate and urine at RT • Oxaliplatin was relatively stable in PUF at -80°C for 28 days • The major radioactive products formed in PUF were monochloro, dicholoro and methionine DACH platin and dihydroxyoxaliplatin (IV)	SPP0085 GLP: No
Human Biotransformation (20 µg/ml)	Human microsomes	Incubation 30 min with or without NADPH	• 30 min following incubation 67% of radioactivity was associated with unchanged drug • another major component (17%) of total radioactivity was diaqua DACH • Similar results were obtained by –NADPH, or using denatured microsomes • Conclusion: formation of these products was non-enzymatic	MIV0249 GLP: No
Human Biotransformation (20 µg/ml)	Bl, Pl, PUF	Incubation 0.1 and 4 hr	• Unchanged drug was the major component in the PUF • Two products present correspond to diaqua DACH platin and methionine DACH platin	MIV0250 GLP: No

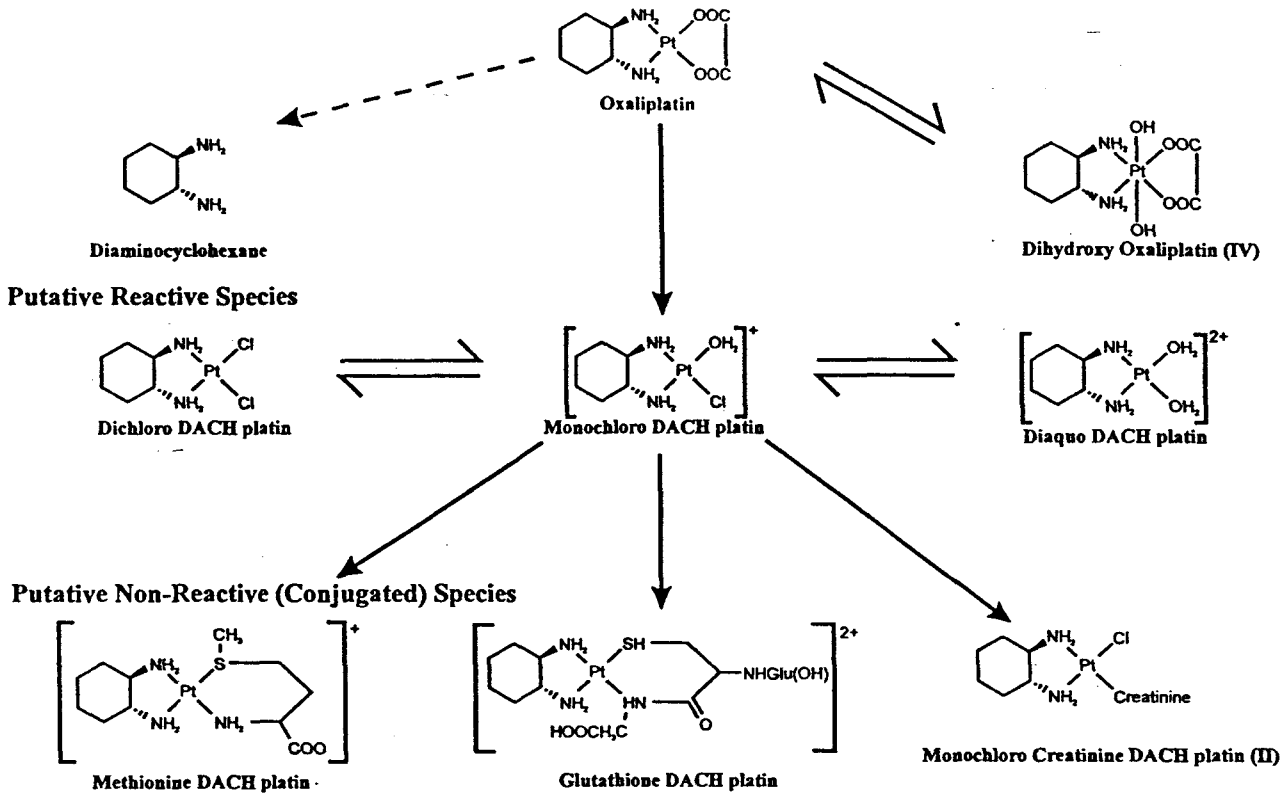
Pl: Plasma; Bl: Blood; PUF: Plasma ultrafiltrate

II. Biotransformation of Oxaliplatin *in vivo*

Species (strain/age) Animal #	Tx Duration /Sampling time	Dose (mg/m^2)	Results Interpretation /Comments	Report No. /GLP /Method
♂ Rat (Wistar, 6-8 wks) # not specified	Single IV dose	48	• Similar types of biotransformation products as seen in *in vitro* studies: $(cysteine)_2$-, methionine-, glutathionine- DACH platin and free DACH	Literature GLP: No
Dogs (Beagle, 2-3 yrs) 4 ♂	Single IV Infusion over 1.5 h Sampling time: predose, 1, 2, 6, 24, 72 and 168 h	72	• Biotransformation was the major clearance mechanism of ^{3}H-Oxaliplatin • PUF: free DACH, monochloro-dichloro DACH platin and 2 unknown species • Urine: 4 major and 7 minor products, free DACH was most abundant • Renal elimination was the major route of excretion in the dog: ~70% dose was eliminated within 24 h of dosing	MET0321 GLP & QA: YES Radioactivity assay by [redacted] metabolite assay by [redacted] and mass spectrometry [redacted]

Pl: Plasma; Bl: Blood; PUF: Plasma ultrafiltrate

The metabolic pathway of oxaliplatin is summarized in the following graph:



Proposed pathway of oxaliplatin biotransformation and putative oxaliplatin biotransformation products

Excretion In all species examined, urine was the primary excretion route. Relatively high urinary levels of oxaliplatin were recovered within 2 h of dosing in rabbits but not other species. In dogs, however, 66% of the dose were excreted within 48 h but at the end of 7 days, radioactivity was still detectable.

Species (strain/age) Animal #	Tx Duration /Sampling time	Dose (mg/m^2)	Results Interpretation /Comments	Report No. /GLP /Method
Rabbits (Japanese white) 4 ♂, 2.5 kg	Single IV Infusion over 1.5 h Sampling time: 1, 3 and 5 h after dosing	44	• Within 24 h, urinary excretion of unchanged and total platinum accounted for 28% and 76% of the dose, respectively • All unchanged oxaliplatin was excreted within 2 h of dosing	ABS0262 GLP: No Oxaliplatin conc. was determined by — UV; total platinum conc. were determined by — spectroscopy
Dogs (beagle) 4 ♂, 2-3 yrs	Single IV Infusion over 1.5 h Sampling time: predose, 0, 1, 2, 6, 24, 72 and 168 h	72	• 77% of the administered radioactivity was excreted within 7 days of dosing • The majority (66% of the dose) was excreted in urine in the first 48 hrs • Fecal excretion acounted for 5-6% of the dose over 7 days	EBA0118 GLP & QA: Yes Radioactivity assays by : —

VI. Toxicology Studies

Single Dose Toxicity Studies

TXA0426 SR96669: A single-dose tolerance study in the rat by oral gavage. (Vol.1.12, p185). Conducted by the sponsor (Sanofi Research, Malvern, PA) with signed and dated GLP and QA compliance statement. The study was completed by March 11, 1998. SR96669 was well tolerated in the rat. The single oral STD_{10} for oxaliplatin was > 600 mg/m^2 in the rat.

species:	Tac:N(SD)fBR rats (5/sex/group)
age; weight:	10 wks; 252-304 g (♂), 172-204 g (♀)
drug:	SR96669 (Clinical formulation, batch 95E16)
vehicle:	purified water
dosage:	0, 25, 50, 75 and 100 mg/kg*
route:	oral by gavage
duration:	single administration
	*dosage is expressed as non saltified compound

Observations

Clinical signs	predosing, five time postdose on D1, then twice daily for additional 13 days
Body weights	predose, and Days 2, 5, 8, 11 and 14
Gross Pathology	D15 at terminal necropsy
Histopathology	not performed

Results

a. Clinical Observations: no mortality incidence
clinical signs: no test article-related clinical signs observed

b. Body weight: minor decrease in body weight gain at HD ♀ D1-4

c. Gross Pathology: no test article-related macroscopic changes

All of other single dose toxicity studies were previously reviewed. These single dose studies are summarized in the following table:

Summary of the Single Dose Toxicology Studies

Study #, GLP Location	Species	Route	N/sex/ dose	Critical Doses	mg/kg	mg/m^2	Significant findings
TXA0427 GLP Vol 1.12/p64	Mouse (CD-1)	i.v. infusion (1 ml/min)	5	LD_{10s} [a]	14-17	84-102	The 3 formulations had the same toxicity (mortality).
				LD_{50s}	16 - 19	96-114	
DDO0604 Non-GLP Vol 1.27/p1	Mouse (CD-1)	2 h i.v. infusion after initial dose of citrate buffer [b] (1-2 ml/min)	5	LD_{10}	28.7	172	
AXA0428 GLP Vol1.12/p122	Mouse (OF1)	i.v. (25 ml/kg)	10	LD_{10}	20	120	
				LD_{50}	22.5	135	
	Mouse (OF1)	i.p. (25 ml/kg)	10	LD_{10}	17.5	105	
				LD_{50}	19	114	
	Rat (Wistar)	i.p. (10 ml/kg)	10	LD_{10}	14	84	
				LD_{50}	17.5	105	
TAX0429 GLP Vol 1.12/p217	Rat (OFA-SD)	IV (2 ml/min)	8	LD_{10}	19-23[c]	114-138	Liver damage seen at autopsy.
				LD_{50}	29	174	

Study #, GLP Location	Species	Route	N/sex/ dose	Critical Doses	mg/kg	mg/m^2	Significant findings
TAX0430 GLP Vol 1.12/p217	Rat (Wistar)	IP	12 ♂	STD10 (Highest non-lethal)	14	84	Oxaliplatin was less toxic (↓ b.w., neurotoxicity and renal toxicity) than cisplatin. Oxaliplatin ↑ AST level (15-25%)
TAX0426 GLP Vol 1.12/p185	Rat Tac:N (SD)fBR	Oral (gavage)	5	Highest non-lethal	100	600	No treatment-related clinical signs
TAX0431 GLP Vol 1.12/p244	Dog (beagle)	IV 2 ml/min, 20 min	0-1	HNSTD	7.5	150	At HD: emesis, diarrhea, ↓ b.w.; proteinuria, hematuria, ↓ WBC and ↑ AST; cardiac toxicity appeared to be the cause of death
				Lethal	10	200	
CVR0146 Non-GLP Vol 1.12/p268	Dog (beagle & mongrel)	IV 5 ml/min 2 infusions at 2.5 h interval	0-2				Oxaliplatin was formulated in saline which results in compound degradation. Oxaliplatin caused death due to metabolic acidosis that led to respiratory arrest

[a] the value range was for three formulations tested: bulk substance, lactose lyophilisate and mannitol lyophilisate

[b] estimated values for mice receiving co-administration of citrate buffer: 50 ml/kg i.v.

[c] the mean LD_{10} for both gender was between 17 (LD_{05}) and 24 (LD_{50}) mg/kg

Summary of the Repeat Dose Toxicology Studies

Study #, GLP Location	Species	Route /Duration	N/sex/ dose	Critical Doses	mg/kg	mg/m^2	Significant findings
DIV0668 GLP Vol1.13/Pg1	Rat (Wistar)	Slow IV 1 ml/min daily × 3	8 ♂	ND[a]			Oxaliplatin was degraded in isotonic saline in these study which made the result not assessable for deriving a critical dose
TXC1025 Yes Vol 1.13/Pg129	Rat (SD)	IV 2 ml/min daily × 3, q21d × 3 cycles	10 & 15	HD = MD = ND[a]	2 1 [redacted]	12 6	1-2 animals died in each group, including a control group, probable due to dosing procedure Oxaliplatin produced ↓ b.w., myelosuppression, dose related kidney necrosis in HD and MD, mild increase in creatinine, urea and ↓ in testes and prostate weight
TXA0621 Yes Vol 1.15/Pg263	Dog (beagle)	1q 28 days or daily × 5, q28d 1-6 cycles Slow IV 2 ml/min	2 or 4	Lethal$_S$ [b] Lethal$_R$ [b] HNSTD$_S$ HNSTD$_R$	10 2 2 1	200 40 40 20	Oxaliplatin produced salivation, emesis, diarrhea, unsteady gait, shaking and trembling; leukopenia and anemia; ↓ testicular weight Ventricular extrasystole and fibrillation in ECG (repeat HD animal died)
TAX0431 GLP Vol 1.12/p244	Dog (beagle)	IV 2 ml/min, 20 min daily × 5	1-2	HNSTD Lethal	7.5 10	45 60	Vomiting, diarrhea, ↓ b.w., ↓ food consumption; proteinuria, hematuria, ↓ WBC and ↑ AST; cardiac toxicity appeared to be the cause of death
TAC1026 GLP Vol 1.12/p244	Dog (beagle)	IV 2 ml/min daily × 5, q28d 3 cycles	3	HNSTD	1.75	35	Slight myelosuppression, dose-related testicular hypoplasia, ↓ testes weight, degeneration of proximal tubules of kidneys; mild to severe pancreatitis
DIV0669 GLP Vol 1.17/p1	Dog (beagle)	2-hr IV infusion (1 ml/min) 1q21days × 3 cycles	3	HNSTD	5	100	150 mg/m^2: 2 deaths may be due to cardiac toxicity (contracted hearts), emesis, salivation, tremors, and uncoordinated movements Dose dependent meylosuppression, testes atrophy
TSA1050 Non-GLP Vol 1.19/p1	Baboon (*Papio cymoce-phalus*)	IV 100 ml/5 min 1 q14/15 days, × 4 doses	1 or 3	HNSTD?	6.1	67	Oxaliplatin was formulated in saline which resulted in degradation No significant clinical , biochemical or hematological toxicity was observed

[a] Not derived; [b] R: repeat dose, S: single dose

Summary of Toxicology Studies

Most of the toxicology studies have been reviewed by Dr. Wendelyn J. Schmidt with the original submission of IND [redacted] and can be cross-referenced. Single dose toxicology studies were performed in mice (i.v., i.p), rats (i.v., i.p. and oral) and dogs (i.v.). Oxaliplatin was found to cause hepatic toxicity to rats (gross pathology of liver damage and ↑ AST). In dogs, target organs for oxaliplatin were the heart (cause of death), GI tract (emesis, diarrhea), liver (↑ AST) and kidney (proteinuria and hematuria). The

acute dose LD_{10}s for mice were 84-172 mg/m^2 (i.v.) and 105 mg/m^2 (i.p.). The LD_{10}s for rats were 114-138 mg/m^2 (i.v.), 84 mg/m^2 (i.p.) and 600 mg/m^2 (oral highest non-lethal). The HNSTD for dogs were 150 mg/m^2. Repeat dose toxicity studies were performed in rats, dogs and baboon, all with i.v. route administration. Oxaliplatin caused myelosuppression, dose-related renal toxicity (kidney necrosis, and urea) and germinal aplasia, ↓ weight testes and prostate. However, ovarian architecture was undamaged.

In dogs, oxaliplatin caused significant cardiac toxicity (ventricular extrasystole and filbrillation in ECG, death due to cardiac failure). Oxaliplatin also caused toxicities in GI tract (vomiting, diarrhea), hematopoietic system (leukopenia and anemia), kidney (proteinuria, hematuria, degeneration of renal proximal tubules), nervous system (unsteady gait, shaking, tremors and trembling), liver (↑ AST, proteinuria) and testis (testicular hypoplasia and ↓ weight) in the dog. Toxicology study in baboons did not generate informative data because the vehicle facilitated drug degradation. The longest duration for the repeat dose studies were conducted in dogs with a schedule of daily × 5 q28 days for up to 6 cycles. The HNSTD for such schedule (daily × 5 q28 days) was 35-45 mg/m^2/day. The lethal doses of oxaliplatin for dogs were 40 (6 cycles) and 60 (1 cycle) mg/m^2/day.

VII. Genetic Toxicology

Summary of Genetic Toxicology Studies

All of the toxicology studies have been reviewed by Dr. Wendelyn J. Schmidt in the Original Pharmtox Review with the original submission of IND [redacted] and can be cross-referenced. In summary, oxaliplatin was negative in the Ames test, but was positive in all other genotoxicity tests, *i.e.*, mouse lymphoma assay for mammalian cells (TK locus), mouse micronucleus assay, and chromosome aberration assay for human lymphocytes in culture. The relative mutagenicity and clastogenicity of oxaliplatin was comparable to cisplatin within an order of magnitude. Oxaliplatin was mutagenic and clastogenic both in the presence or absence of metabolic activation.

IX. Reproductive and Developmental Toxicology Studies

FER0311 Fertility and reproductive study following sequential intravenous administration in the rat (Vol.1.19, p26). Conducted by sponsor at TRISA in France as a GLP study with signed and dated QA compliance statement. The study was completed by Feb. 8, 1993.

Conclusions from this study: when administered prior to mating, oxaliplatin

1. induced significant increase in the number of post-implantation losses (97% total resorption) in HD ♀s (2.0 mg/kg/day)
2. induced early resorption in HD ♀s; the mean percentage of resorptions in relation to the total number of implantation was 96%
3. did not give rise to any malformations in rats
4. did not affect the postnatal development and reproductive function for the F1 generation

species:	Sprague Dawley rats (40/sex/dose group for F0 generation) *F1 animals were not treated and the females gave birth to F2 offspring*
age; weight:	*age not specified*; mean body weight = 216 g
drug:	Oxaliplatin (batch 91-012)
vehicle:	5% isotonic dextrose solution
dosage:	0, 0.5, 1.0 and 2.0 mg/kg/day (0, 3, 6 and 12 mg/m^2/day)
route:	I.V. under light ether anesthesia

duration: daily × 5, q21d per course,
× 3 courses for ♂s before mating (63 days total)
× 2 courses for ♀s, mating occurred at the end of the first course of treatment

Observations

Clinical signs daily before and after treatment
Body weights predose, and once weekly
Food and water consumption recorded daily by visual inspection
Mating vaginal smears performed daily until simultaneous detection of spermatozoa and cells indicating a favorable point in the cycle (estrus, post-estrus)
Necropsy all F0 animals

Fertility and General Reproductive Performance		
F0 animals examined	**# of animals examined per dose group**	**# of F1 offspring mated**
Cesarean section (D20 gestation)	20	
Spontaneous delivery	20	2 pups/sex/litter were kept on weaning these F1 animals were mated to assess the reproductive function

Gross pathology for all F0 animals at necropsy
Development of F1 pups mortality and clinical signs
malformations
Reproduction of F1 pups four days after parturition, the F2 females were sacrificed, necropsied and all abnormalities noted

Results

a. Clinical and behavioral observation: no treatment-related mortality for ♂s
2/20 HD ♀s died on gestation day 16 following total resorption of their uterine content; the remaining were sacrificed on gestation D20

no clinical or behavioral abnormalities

b. Body weight: the weight difference between groups was minimal in ♂s
the between-group variation of body weight became highly marked for ♀s during the gestation period: ↓28% in HD ♀s compared to the control

c. Food and Water Consumption: no treatment-related changes

d. Fertility and General Reproductive Performance (include both C section and spontaneous delivery): In HD ♀ group, 36/37 presented with total resorption of uterine content

Cesarean section:

Groups	Control	LD	MD	HD
Dosage (mg/kg/day)	**0**	**0.5**	**1.0**	**2.0**
Parents (F0)				
♀s with sperm	18/20	18/20	17/20	18/20
Pregnancies	17/18	16/18	15/17	18/18
Litters (F1) [a]				
Corpora lutea	17.8	17.3	17.4	17.9
Implantations	14.8	13.4	15.6	15.8
Live fetuses	12.9	12.5	12.9	0.2 [b]
Dead fetuses	0.1	0.2	0.4	0.0
Early resorptions	1.8	1.8	3.0	15.3
Weight of fetuses (g)	3.57	3.89	3.89	2.68
Sex ratios of fetuses (♂/♀)	1.13	1.04	1.14	1.00

[a] Numbers represent the arithmetic mean for each group; 19/20 dams had complete resorption of uterine contents, 0.2 is 4 live fetuses in one of the 20 ♀s

Spontaneous delivery:

Groups	Control	LD	MD	HD
Dosage (mg/kg/day)	**0**	**0.5**	**1.0**	**2.0**
Parents (F0)				
♀s with sperm	19/20	19/20	18/20	19/20
Pregnancies	17	18	17	19
♀s with delivery	17	18	16	0
Litters (F1) [a]				
Implantations	15.4	16.0	14.5	14.1
Live births	13	10.6	9.7	0
Stillbirth	0.3	0.8	0.3	0
Survivors D4 postpartum	13.5	11.2	9.4	0
Survivors at weaning	8.0	7.8	7.5	0
Weight at birth (g) ♂ + ♀	7.37	7.57	7.25	0
Weight at weaning (g)	56.6	59.6	53.6	0
Sex ratios of live newborns (♂/♀)	0.96	0.96	0.94	0

[a] Numbers represent the arithmetic mean for each group

e. Gross pathology no macroscopic findings for F0 animals

f. Malformation: no abnormalities

g. Development and Reproduction of F1 pups
no abnormal changes in weight gain, behavioral development and reproductive function, the course of gestation in F1 ♀s and condition of F2 offspring during the first days of lactation

TER0307 Teratogenesis trial by intravenous administration in the rat. (Vol.1.20, p208). Conducted by sponsor at TRISA in France as a non-GLP study. The study was completed by May 2, 1995. Conclusions from this study are that oxaliplatin:

1. caused a growth delay (↓ weight and ossification delay) in the fetuses of rats dosed at days 6-10
2. did not induce any significant malformation
3. ↑ early resorptions, d6-10 and d11-16

species: Sprague Dawley E. O. P. S. rats (10/mated ♀s/group for F0 generation)
age; weight: 3-6 months; mean body weight = 337.3 g
drug: Oxaliplatin (batch D91-012)
vehicle: 5% sterile glucose solution
dosage: 0 and 1.0 mg/kg/day (0 & 6 mg/m^2/day)
grouping:

Treatment				Schedule
Groups		Groups		(day of gestation)
A	Vehicle control	*1*	Oxaliplatin	D1-5
B	Vehicle control	*2*	Oxaliplatin	D6-10
C	Vehicle control	*3*	Oxaliplatin	D11-15

route: I.V. (5 ml/kg) via caudal veins under light ether anesthesia
duration: daily × 5, during gestation at one of the 3 phases (D1-5, D5-10 and D11-15)

Observations

Maternal Responses

Clinical signs and mortality — daily
Body weights — determined randomly during gestation days 0, 6, 12, 16 and 20
Food and water intake — recorded daily by visual inspection
Hysterectomy — at D20 of gestation

Fetal responses

Viability, litter size, body weights, and examination for external and internal malformations

Results

a. Maternal Response

Clinical signs: no treatment-related clinical or behavioral abnormalities
Mortality: no mortality was observed
Body weight: ↓ 4% beginning on D12 of gestation in group 2 *vs.* the matching control group B
Food intake: no abnormality
Hysterectomy: no increase in pre- and post-implantation losses

Hysterectomy Data Summary:

Groups	*Controls (A, B, C)*	1	2	3
Dosage (mg/kg/day)	*0*	1.0	1.0	1.0
Dosing period (Days)	*D1-5, D6-10, D11-16*	D1-5	D6-10	D11-16
Parents (F0)				
Mated ♀s	*10, 10, 10*	10	10	10
Pregnancies	*6, 6, 9*	9	5	4
Evaluated pregnant ♀s	*6, 6, 9*	9	5	4
Litters (F1) [a]				
Corpora lutea	*19.3, 15.8, 16.9*	15.4	17.6	21.0
Implantations	*15.2, 12.2, 11.0*	11.3	12.6	13.0
Pre-Implantation loss %)	*21, 22, 34*	30	27	32
Live fetuses	*12.7, 9.3, 8.7*	9.6	9.0	13
Dead fetuses	*0, 0, 0*	0	0	0
Early resorptions	*2.5, 2.2, 2.2*	1.6	3.4	3.3
Late resorptions	*0, 0.7, 0.1*	0.2	0.2	0.0
Length of fetuses (cm)	*4.32, 4.25, 4.53*	4.24	4.05	4.21
Weight of fetuses (g)	*3.8, 3.9, 4.0*	3.93	3.08 [b]	3.67
Sex ratios of fetuses (♂/♀)	*0.77, 1.07, 1.23*	0.83	1.14	0.86

[a] Numbers represent the arithmetic mean for each group; [b] significant difference at $p < 0.05$